Appendix J: Health economics

J.1 General

Economic evidence to support decision making for a clinical review question begins with a systematic search of the literature. The aim of this is to identify any published economic evaluations of relevance to the topic of interest. At this stage it may become apparent that evidence exists in the literature that meets the review question criteria; in this event, there is no need for original economic analysis. If no such literature is available, it may be decided that original economic modelling can generate useful evidence. The aim is to produce a cost–utility analysis in order to weigh up the benefits and harms of comparable interventions. The extent to which this is possible will depend on the availability of evidence with which to define the clinical pathway and disease natural history and estimate the benefits, harms and costs of competing courses of actions.

J.2 Topics prioritised for health economic modelling: risk stratification, prevention strategies and frequency of follow-up in patients with or at risk of diabetic foot problems

J.2.1 Decision problem

Table 1: Review questions

Review Question 4 (See appendix C and section 4.4 of the full guideline)	What are the clinical utilities of assessment and risk stratification tools for examining the feet of people with diabetes and classifying risk of foot problems?
Review Question 5 (See appendix C and section 4.5 of the full guideline)	How often should people with diabetes who are at risk of developing foot problems be reviewed?
Review Question 6 (See appendix C and section 4.6 of the full guideline)	What is the effectiveness of different prevention strategies for people with diabetes at risk of developing foot problems?

The GDG identified 3 research questions as priority areas for economic analysis. The questions form a convenient unit for analysis. Risk assessment implies an accepted understanding that care and expenditure on preventative interventions should be differentiated and targeted to those patients at greatest need. If patients are to be differentiated in terms of risk, it may be appropriate to adopt different intervals between follow-up review appointments.

Table 2: PICO

Population	All patients with diabetes mellitus
Intervention	Bespoke and off-the-shelf orthotic footwear
Comparator	Usual/standard foot-care
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of bespoke and off-the-shelf orthotic footwear

Patients who are at risk for foot ulcers receive a spectrum of interventions to mitigate their risk factors. This includes podiatry services, education on foot and nail care, and the provision of specially fitted footwear and orthotic inserts. These bespoke orthotics are designed to (where needed) relieve areas of excessive pressure; reduce shock and shear forces; accommodate, stabilize and support deformities and limit motion of joints (American Foot & Ankle Society, 2014). The provision of orthotic footwear on the NHS includes a requirement to fit, repair or provide a new pair of bespoke orthotic inserts and shoes on an annual basis for the remainder of the patient's lifetime and therefore has long-term recurrent costs. There is currently uncertainty about whether orthotic footwear should be given to all patients regardless of their risk of ulceration, or whether the intervention should be targeted at patients with a particular level of risk.

This economic evaluation aimed to assess the cost-effectiveness of providing custom orthotic footwear (shoes and inserts) to patients at low, moderate and high risk of developing foot ulcers. The analysis considered the cost perspective of the NHS/PSS as per the NICE reference case.

J.2 Systematic review of published cost–utility analyses

J.2.1 Methods

We conducted a systematic literature search in order to identify published cost–utility analyses that provide evidence of the cost effectiveness of the interventions in question.

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of preventative measures including information, advice and education about self-monitoring and preventing foot problems; appropriate footwear, provision of foot orthoses and skin and nail care. We also considered studies that examined the cost effectiveness of risk assessment strategies, and those that examined the utility of different lengths of follow-up.

Search strategy

The search strategy was based on that used to identify clinical evidence for these questions, with the RCT filter removed and a standard economic filter applied (see appendix D).

Quality appraisal

Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the Guidelines Manual (2013).

J.2.2 Results

Study identification

We identified 3 studies of potential relevance through title and abstract screening. On perusal of the retrieved papers, 2 cost–utility analyses were identified which considered preventative care strategies consistent with those identified in the review protocol for RQ6 (see section 4.6 of the guideline). The third, a CUA by Rauner (2005) was a straight forward translation of the Ragnarson-Tenvall (2001) study to an Austrian healthcare setting, and therefore differed only in terms of cost inputs. Therefore we refer in detail to the original Ragnarson-Tenvall model instead in the summary tables that follow. No cost–utility analyses were identified that considered different periods of review (see section 4.5 of the guideline) or examined the cost-effectiveness of risk stratification schemes directly (see section 4.4 of the guideline).

Quality and results of included studies

Details of the design, quality and results of included studies are detailed in Table 3.

Table 3: Economic evidence tables – prevention of diabetic foot ulcers

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Ragnarson-Tennvall et al. (2001) Simulated cohort of 10,000 Swedish DM patients **Partially applicable[a]** **Very serious limitations[b,c,d,e,f]**	Effects: Scenario analysis which simulates the effectiveness level at which intervention becomes CE Costs: surgery, impatient care, rehabilitation, prosthesis, social/homecare costs of amputation included. Discounted at 3%pa (basecase) and 5% pa (SA) Utilities: Taken from published HRQol studies of diabetic foot.	Markov model with 5yr time horizon Current practice vs enhanced model of care comprising education, footwear, podiatry. Patients defined as 1 of 3 age and 4 risk cohorts according to the IWGDF classification. Interventions tailored to risk. Outcomes reported as ulcer incidence, amputations, costs and QALYs Patient leaves the model after primary major amputation (a 1-foot model)	£4917 on average (min: €530, max €13,072 depending on risk and age)	QALY gains across all risk groups are moderate (mean 0.02)	Treating moderate- and high-risk patients is cost saving (dominating)	For high-risk patients, enhanced care is cost-saving if it reduces both foot ulcers and LEA by 25%. Lower-risk groups incurred higher costs (180-400 Euros) to achieve the same level of effectiveness.	In a one-way sensitivity analysis, varying the discount rate between 0–5% had no impact. If the intervention lowered foot ulcer rates by 25% but had no impact on LEA rates, the most cost-effective strategy was to treat risk groups 3-4 (moderate-to-high risk) in all age groups but not the highest risk groups (who experience more amputations).

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Ortegon et al. (2004). Simulated cohort of 10,000 Dutch DM patients **Partially applicable[a]** **Very serious limitations[b,d,e,g]**	Effects: Scenario analysis which simulates the effectiveness level at which intervention becomes CE Costs: Direct medical costs only. Included: expenses such as labour, medication, laboratory, materials (shoes, insoles, contact casts), and procedure (diagnostic tests, debridement, bone resection). Cost in $US Utilities: Taken from published HRQoL studies of diabetic foot.	'Optimal foot care' OFC, including professional protective foot care, education of patients and staff, regular inspection of the feet, identification of the high-risk patient, treatment of nonulcerative lesions, and a multidisciplinary approach to established foot ulcers. Improved glycaemic control (ICG) effect based on UKPDS. Considered separately and combined. Patients defined as 1 of 3 age and 4 risk cohorts according to the IWGDF classification.	A 10% reduction in foot lesions costs an extra $2,210 over the lifetime of the patient	Incremental gain of 0.09 QALYs	For patients receiving IGC+OFC, ICER ≤$25,000 per QALY gained (relative to standard care).	'Management of the diabetic foot according to guideline-based care improves survival, reduces diabetic foot complications, and is cost-effective and even cost saving compared with standard care'	'Increasing the effectiveness of preventive foot care in patients under OFC and IGC+OFC resulted in more QALYs gained, lower costs, and a more favorable ICER'. No further details given

(a) Non- NHS/UK Setting
(b) Model structure limited to one foot and omits critical aspects of health condition (multiple amputations, some considerations of ulcer aetiology, HRQoL of different ulcer types and outcomes)
(c) Time horizon (5 year) too short to capture important differences and lifetime costs of interventions
(d) Effectiveness of interventions assumed and explored through scenario analysis, not based on trial evidence
(e) No PSA
(f) deterministic sensitivity analysis not comprehensive
(g) deterministic sensitivity analysis results discussed but not reported

J.2.2.13 Discussion

The evidence obtained from published economic evaluations was not sufficient to provide guidance to answer the review question. Limitations of these studies included a lack of precise information on the parameterisation of the effectiveness of interventions, using an exploratory approach instead which examined the threshold of effectiveness (in terms of ulcers and amputations avoided, and associated QALYs saved) at which these interventions become cost effective. These analyses were also single-foot models, which terminated after the first occurrence of a major amputation.

J.2.3 Original cost–utility model – methods

J.2.3.1 Overview of the model

Modelled population(s) and intervention(s)

Table 4: Economic model PICO

Population	All Patients with Diabetes Mellitus stratified by ulceration risk
Intervention	Bespoke or “Off-the-Shelf” orthotic shoes and inserts
Comparator	No orthotic shoes or inserts
Outcomes	Quality adjusted life years

Given the absence of relevant, high-quality evidence in the published literature, we developed a de novo Markov model to assess the cost effectiveness of providing custom orthotic footwear (shoes and inserts and education on their use) to patients at low, moderate and high risk of developing foot ulcers. No economic evaluation of risk assessment could be found in the existing literature, and the clinical evidence was insufficient to parameterise an analysis of risk assessment compared with some control measure. Therefore, our model assumes at the start that all patients receive a risk assessment by an appropriately trained professional. It was envisioned that the model would demonstrate the utility of risk assessment indirectly should it find that targeting patients at a particular risk level was cost effective compared with providing the intervention to all patients regardless of risk. Unfortunately, different lengths of screening interval could not be modelled because of a lack of clinical evidence in this area (see section 4.5 of the guideline). Therefore the de-novo model could not provide a health economic answer to this issue.

Model structure

We built a Markov model with a monthly cycle-length and a lifetime time horizon, which incorporates the health states described Table 5. A schematic depiction of the model structure is given in Figure 1. The model uses a patient perspective for outcomes and an NHS perspective for costs, in line with the Guidelines Manual (2012).

Table 5: Modelled health states

Health state	Definition
Low risk	An ulcer-free disease state, with a low probability of transitioning to an ulcer state.
Moderate risk	An ulcer-free disease state, with an increased probability of transitioning to an ulcer state given the natural history of diabetic foot problems described in Leese, (2006)
High risk	An ulcer-free disease state, reflecting previous ulcer history or natural history of diabetic foot problems described in Leese, (2006)
Low risk with ulcer	An active ulcer state having transitioned from a low risk of ulceration
Moderate risk with ulcer	An active ulcer state having transitioned from a moderate risk of ulceration
High risk with ulcer	An active ulcer state with associated with being at high risk
High risk post-minor amputation	A state which preserves the memory of a minor-amputation (part of limb or toe, below the ankle) history and associated risk level
High risk-post major amputation	A state which preserves the memory of a major-amputation (entire foot above ankle) history and associated risk level
Post minor amputation with ulcer	An active ulcer state which preserves the memory of a minor-amputation history and associated risk level
Post major amputation with ulcer	An active ulcer state which preserves the memory of a major-amputation history and associated risk level
Double amputee	A state reflecting a history of two major (above ankle) amputations
Death	A state describing death from all causes, including the mortality that occurs as a result of ulceration.

Markov models are useful for modelling disease processes in a time-explicit manner. In a Markov model, the disease process is partitioned into distinct states with transitions between states occurring according to given transition probabilities over a discrete time period known as a cycle. Markov states can have estimates of resource use and quality of life attached to them, so that long-term costs and outcomes can be calculated by running the model over an appropriate number of cycles. Interventions which may, for example, reduce mortality or healing rates can therefore readily be evaluated in this framework by making appropriate evidence-based adjustments to the relevant transition probabilities, costs and health outcomes.

In this model, a theoretical cohort of patients with diabetes mellitus undergo risk stratification according to the criteria outlined in Leese et.al (2006 – see Table 7 in this appendix). The GDG recommended that this schema should be used for risk assessment (see guideline section 4.4). Subsequent to this risk assessment, patients remain in an ulcer-free condition and maintain their current level of risk, develop an ulcer, or increase their risk level. Patients who develop an ulcer can undergo a minor or major amputation, heal, or persist with the ulcer. Per the risk-assessment criteria, any patients who heal move to the high-risk category in the next cycle, in order to reflect their ulcer history. For patients who undergo an amputation, the model includes two subtrees in order to capture their history of amputation. These subtrees reflect a post major or minor amputation disease stage, and also classify the patients as high risk in line with the risk assessment tool. In this way, the model captures the post-amputation natural history of diabetic foot problems which is absent from published economic analyses. Patients may then develop further ulcers and have subsequent minor amputations and healing. For patients who have had a major amputation, any further major

amputation means a transition to the double major amputee state, from which no further ulcerations are possible. Any ulcers which occur on a post-major amputation site are not accounted for in this model as ulceration on remaining limb stumps is beyond the scope of this guideline. The model runs on a monthly cycle length for the remaining life expectancy of a cohort of patients with a mean age of 60 years. The mean age of 60 was based on discussions with the GDG and reference to other models. Diabetic foot problems in young people are exceptionally rare, since the occurrence of risk factors for ulceration are correlated with the time a patient has diabetes. Previous analysis, such as the UKPDS and CORE models have used a similar mean age. A life expectancy time horizon was chosen because the patients receiving orthotic shoes and inserts will require a new set each year for the rest of their lifetime. A monthly cycle was considered appropriately short to capture the important pathological changes in diabetic feet whilst remaining computationally manageable, and was selected following consultation with the GDG. Costs associated with the provision of orthotic shoes and inserts are attached to the intervention arms as per the four scenarios considered. Quality of life decrements and costs are associated with ulceration and amputation states. Both costs and benefits are discounted at 3.5% per year as per the NICE reference case.

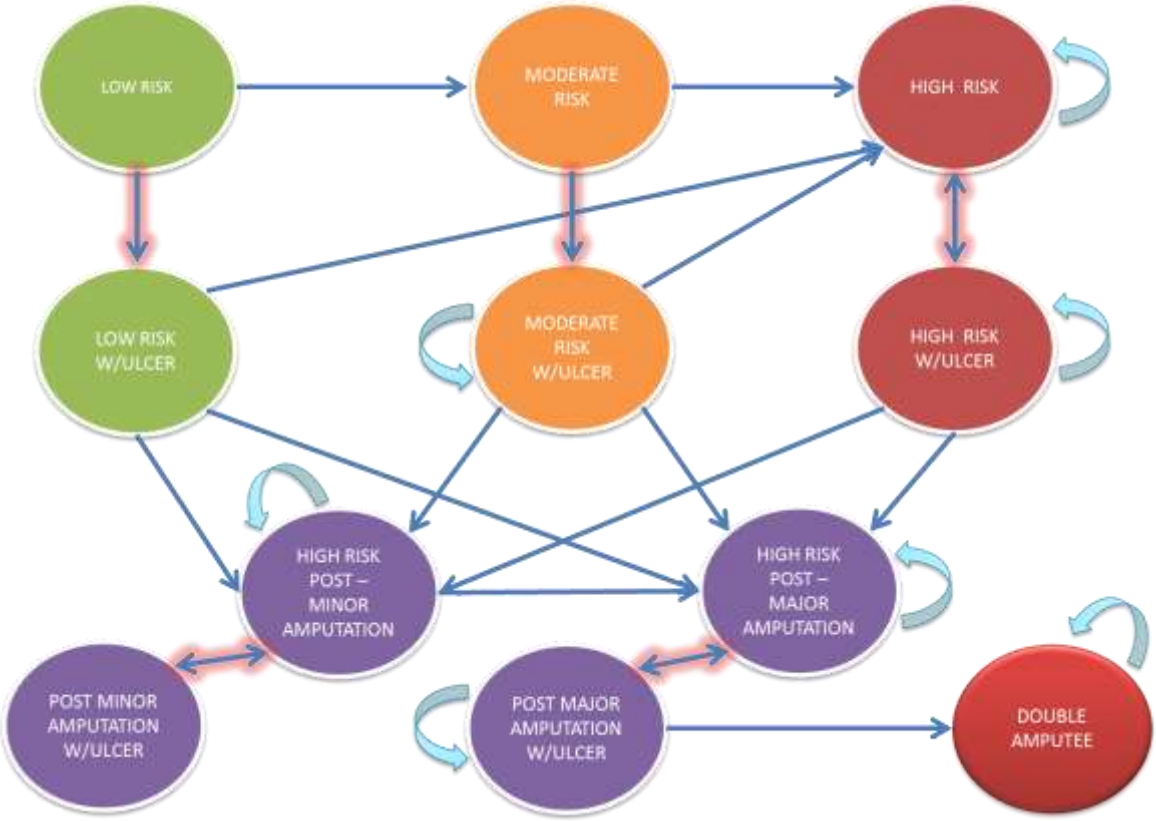

Figure 1 Structure of original cost–utility model – Red transition arrows indicate transitions that are directly influenced by the intervention.

Key assumptions

There are a number of assumptions built into the economic model which need to be considered when analysing the results generated. These are summarised in Table 6.

Table 6: Key assumptions of original cost–utility model

- All patients undergo a risk assessment at the start of the model. There was no clinical evidence available to compare a risk assessment vs no-risk assessment cohort. Additionally, it was not possible to parameterise a cohort of patients in a no risk assessment arm in terms of their disease progression, since all available data on rates of healing vs non-healing, ulcer severity and infection are taken from patients who are known to healthcare services. Modelling the progression of an unseen disease process is difficult in the absence of data on presentation rates of patients at different follow-up intervals.
- As a consequence of their risk factors, low-risk patients tend to develop less complex ulcers with shorter healing time whilst patients at moderate/high risk develop more severe ulcers which take longer to heal.
- Different definitions of minor and major amputations exist in the literature. For the purposes of this model, a minor amputation is defined as the removal of any part of the foot below the ankle, whereas a major amputation is defined as a removal of the foot above the ankle. Patients can experience multiple minor amputations, but only two major amputations can occur in a lifetime.
- Whilst we consider different probabilities of healing for more/less severe ulcers in our model, we do not consider the very broad spectrum of individual treatment durations (and varying costs) that a patient may require once they ulcerate, instead assuming that this spectrum is accounted for in the average cost (and uncertainty estimates around it). A more detailed analysis is not easily undertaken in a Markov model framework and would be better suited to an individual patient simulation. Currently there are insufficient data to parameterise such a model.
- To provide a proxy for likelihood of risk progression from low to moderate risk, we assumed that the first risk factor low-risk patients develop is diabetic neuropathy (as per the figures reported by Partanen et al., 2005). Peripheral neuropathy affects >30% of the diabetic population and leads to dry skin, reduced joint mobility and loss of protective sensation that would otherwise detect physical injury – all factors which predispose an individual to ulceration (Wu et.al 2007).
- For moderate-risk patients, we used the development of peripheral vascular disease to indicate an elevation of ulceration risk from moderate to high. Macrovascular disease is commonly associated with infection, and these factors reduce the probability of ulcer healing and increase the likelihood of amputation (Prompers, 2007). Whilst this is a simplification which ignores the development of other risk factors such as deformity (although these are considered in the patients' baseline risk assessment), it is consistent with our assumptions that lower-risk patients tend to develop less complicated foot problems whereas higher risk patients tend to have more complex, difficult-to-heal ulcers.
- Whilst, in different scenarios, the model differentiates between the effectiveness of bespoke and off-the-shelf orthotics, the base case uses the same average cost for both interventions. Whilst the effect of this is explored in the sensitivity analysis, it is likely to penalise the less effective intervention in the base case (which may in reality be significantly cheaper). Unfortunately no data on average cost of off-the-shelf orthotics were available, and the GDG stressed that it may be a very wide-ranging cost, reflective of the highly variable specification of such footwear. We assumed that after an amputation patients still receive the intervention (or a bespoke orthotic plus a shoe to fit their prosthetic) and that therefore the intervention still had an impact on their likelihood of getting an ulcer on their feet/foot, either the on one foot that had a minor amputation or the contralateral healthy foot, or on the contralateral limb if they had had a major amputation.

J.2.3.2 Parameters – general approach

Identifying sources of parameters

With the exception of the effectiveness estimates of orthotics, inserts and education, which were drawn from the systematic review conducted for this research question (see below), parameters were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for quality of life, resource use and cost parameters in particular, we conducted searches in specific databases designed for this purpose – the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED), for example.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review (see J.2.2.2, above); during the review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data were obtained from unpublished sources; further details are provided below.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

J.2.3 Model Parameters

Epidemiological parameters were obtained via a literature review of published studies and exploring available national statistics and health outcome databases.

Risk assessment

Based on the evidence presented to the GDG for RQ 3, we used the risk assessment criteria presented by Leese, (2006) as the basis of risk assessment in our simulated cohort. This risk score is based on 5 criteria identified as key clinical predictors of ulceration in a UK based study (Abbott, 2002). Ulcer rates for 3526 patients are reported after 1.7yrs of follow up in the Leese et al. (2006) paper. The risk assessment criteria are summarised in Table 7.

Table 7 Risk assessment criteria (Leese et al., 2006)

Low Risk	Moderate Risk	High Risk
Able to detect at least one pulse per foot **AND** Able to feel 10g monofilament **AND** No foot deformity, physical or visual impairment	Unable to detect both pulses in a foot **OR** Unable to feel 10g monofilament **OR** Foot deformity **OR** Unable to see or reach foot	Previous ulceration or amputation **OR** Absent pulses AND unable to feel 10g monofilament **OR** One of above with callus or deformity

We also used the follow-up data on ulceration outcomes in Leese (2006) to derive ulceration rates. Probabilities of ulcer occurrence were derived from these ulceration rates in each risk category (see table 8).

Risk Progression

Whilst the majority of patients are low risk, over the course of their lifetime some will develop conditions such as neuropathy, ischaemia, or Charcot deformity which will elevate their risk level. Longitudinal studies which examine the incidence of these factors for specified follow-up periods after a patient's initial risk assessment are absent from the literature. However there are data on development of risk factors in diabetic patients independent of risk stratification. Therefore, to provide a proxy for likelihood of risk progression, we assumed that the first risk factor the majority of low-risk patients develop is diabetic neuropathy as per the figures reported by Partanen et Al. (2005). Peripheral neuropathy affects >30% of the diabetic population and leads to dry skin, reduced joint mobility and loss of protective sensation that would otherwise detect physical injury – all factors which predispose an individual to ulceration (Wu et.al 2007). For moderate-risk patients, the development of peripheral vascular disease was used to indicate an elevation of ulceration risk from moderate to high. Macrovascular disease is commonly associated with infection, and these factors reduce the probability of ulcer healing and increase the likelihood of amputation (Prompers, 2007). Whilst this is a simplification which ignores the development of other risk factors such as deformity (although these are considered in the patients' baseline risk assessment), it is consistent with our assumptions that lower-risk patients tend to develop less complicated foot problems whereas higher-risk patients tend to have more complex, difficult-to-heal ulcers.

Ulcer healing rates

Zimmy et al. (2002) reported ulcer healing rates according to ulcer aetiology. We assume that low-risk patients tend to develop less complex, neuropathic ulcers with shorter healing times, whilst patients at moderate/high risk develop more severe ischaemic ulcers, which take longer to heal. We converted these healing times into per-cycle healing probabilities for incorporation into the Markov model (see Table 8).

Amputation

Foot ulcers are the most common cause of lower-limb amputation (Diabetes UK, 2012). We used the amputation rates reported by Oyibo et al. (2001) (see table 8), as this study referred to amputation rates according to ulcer severity (described using the University of Texas grading scheme recommended by the GDG) and the level of amputation performed (minor, major). We found that different definitions of minor and major amputations exist in the literature. For the purposes of this model, a minor amputation is defined as the removal of any part of the foot below the ankle, whereas a major amputation is defined as a removal of the foot above the ankle.

Table 8: Natural history parameters

Parameter	Description	Value (95%CI)	Source
Proportion of patients at low, moderate or high risk	We used the numbers of patients in each risk stratum reported by Leese (2006) and used these as alpha parameters in a Dirichlet distribution.	64% (low risk), 22% (moderate risk), 14% high risk)	Leese et al. (2006)
Proportion of patients who ulcerate when low, moderate or high risk	Percentages converted to rates over the 1.7yrs of follow-up in the source study, then transformed to monthly per-cycle probabilities.	0.36% (low), 2.3% (moderate), 29.4% (high)	Leese et al. (2006)

Parameter	Description	Value (95%CI)	Source
Neuropathic ulcer healing time (days)	Monthly healing probabilities calculated using the using the ratetoprob function in TreeAge Pro: Ratetoprob(1/D*(365.24*CycleLength))	77.7 (62, 93)	Zimmy et al. (2002)
Ischaemic ulcer healing time (days)	Monthly healing probabilities calculated using the ratetoprob function in TreeAge Pro: Ratetoprob(1/D*(365.24*CycleLength))	133 (116, 149)	Zimmy et al. (2002)
Increase risk level (low to moderate)	Monthly probability calculated from the incidence rate of neuropathy taken from a cohort 10 years post diagnosis. Ratetoprob(iN*(1/10*CycleLengh))	42% at 10yrs post diagnosis	Partanen et al (2005)
Increase risk level (moderate to high)	Monthly probability calculated from the incidence rate of peripheral vascular disease taken from a cohort of type 2 diabetics: Ratetoprob(PVD*(1/15*CycleLength))	6% at 15yrs post diagnosis	Adler et al. (2007)
Probability of amputation at low risk w/ulcer	Monthly probability calculated from the amputation rates in the lowest UT grade ulcers reported by Oyibo et al (2001) Probtoprob (dpalr*(1/0.5))*CycleLength)	0.0329	Oyibo et al (2001)
Probability of amputation at moderate or high risk w/ulcer	Parameterised from the amputation rates in the more severe UT grade ulcers reported by Oyibo et al (2001)	0.2621	Oyibo et al (2001)
Probability an amputation is major/minor	Parameterised from the number of major amputations reported by Oyibo (2001) fitted to a beta distribution. The probability of minor amputation is the complementary probability to this value.	0.24	Oyibo et al (2001)

[a] D = healing rates
[b] iN =Incidence rate of neuropathy at 10yrs
[c] PVD = Incidence rate of peripheral vascular disease
[d] dplar = probability of amputation at low risk
[e] UT = University of Texas wound classification system

Mortality

Within a cycle, patients can die due to their background mortality risk or can die from a complication relating to their foot problem. Mortality from all other causes, which are not represented explicitly in the model, is estimated using national mortality statistics (ONS 2012-2013 life tables, ONS, 2014). Diabetes is an age- and sex-specific risk factor for premature mortality, so the mortality rates in the life tables were multiplied by the additional hazard of death experienced by people with diabetes (we used that described by the Yorkshire and Humber Public Health Observatory [YHPHO] NHS National Diabetes Support Team, 2008 – see table 8).

Table 9 Age and sex specific mortality hazards for diabetes

Sex	Age	Hazard ratio
Male	20-39yrs	2.54
	40-59yrs	2.17
	60-79yrs	1.91
Female	20-39yrs	3.76
	40-59yrs	2.54
	60-79yrs	2.53

Several studies have pointed to the increased risk of death from, for example, cardiovascular disease in patients with foot ulcers. Therefore, we incorporate an increased mortality risk associated with the development of a foot ulcer and any subsequent amputation(s) (Moulik et.al 2003 – see table 14). Multivariate analyses have suggested that the hazard ratio for mortality following ulceration and the hazard ratio for mortality following amputation are not statistically significantly different, and therefore we use only the hazard ratio for ulceration throughout. A history of amputation does carry an increased risk of further amputation, and this is reflected in our model using the hazard ratios reported by Lipsky (2011 – see table 14).

J.2.3.4 Intervention effects

The clinical effectiveness of bespoke and off-the-shelf footwear, inserts and education on their usage were drawn from the clinical evidence review presented in Appendix H Section 6.3. We transformed these into odds ratios for computational ease in the model.

Table 10: *Relative risk of ulceration with the two intervention strategies*

Intervention	Relative risk (95% CIs)	Equivalent odds ratio (95% CIs)
Bespoke orthotic footwear, inserts and education	0.34 (0.23, 0.5)	0.221 (0.131, 0.370)
Off-the-shelf orthotic footwear, inserts and education on their use	0.55 (0.42, 0.70)	0.418 (0.291, 0.601)

J.2.3.5 Costs

We obtained the cost of each of the resource use elements in the model from a number of standard sources. Where these sources did not provide the unit cost needed to parameterise the cost of a resource use variable in the model, we conducted a search for unit costs generated from costing studies or in trials. We used NHS Reference Costs as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information.

The Personal Social Services Research Unit (PSSRU) generates the Unit Costs for Health and Social Care report which includes costs for both community and hospital-based healthcare staff.

Where an appropriate reference cost could not be sourced from national tariffs and the cost variable used was from a relevant published study, we inflated the value to current prices using the HCIS inflation indices.

For ulcer events, the model applies a mean cost encompassing inpatient and outpatient costs (see Table 12) to the first ulcer state a patient enters. Patients cannot experience multiple ulcerations simultaneously; therefore, they only accrue additional costs if they heal and develop subsequent ulcers or undergo amputation. For amputation events, there is a cost associated with the amputation procedure taken from the appropriate HRG, and post-amputation care costs (see table 12) are then applied pro-rata for the remaining life

expectancy of the patient. To cost the amputation procedure, we used relevant HRG codes for major and minor amputation to derive weighted average costs, calculating the standard deviation of the expected value from the IQRs in the NHS reference costs and using this to parameterise a gamma distribution, which we then sample from in the PSA to explore uncertainty. Kerr et al. (2014) detail outpatient and community costs for foot ulcers that incorporate dressings, antibiotic therapy, podiatry services, off-loading, district nurse and GP/practice nurse care, imagery and patient transportation costs. These costs are partitioned between patients who have less severe ulcers (that is excluding those patients with ulcers extending to tendon, periosteum or bone, and those with infections of bone, soft tissue infections requiring systemic antibiotics, gangrene, critical renal disease, severe peripheral arterial disease and other complications including Charcot) and those who have more severe ulcers (those patients exhibiting the previously described characteristics not present in less severe patients). We assume that patients who are at moderate or high risk of ulceration will experience more severe ulcers, whereas patients at low risk will experience less severe ulcers. This is consistent with the breakdown of costs assumed in the Kerr et.al 2014 study, where 60% of patients are assumed to have less severe ulcers. In our model, approximately 60% of patients are assumed to be low risk at the time of assessment in the base case. We removed the cost of orthotics and bespoke shoes from the costs presented in Kerr et.al (2014) (to ensure no double-counting of the intervention costs) and this gives an average ulcer cost (outpatient and community care only) per patient of £3,221 for less severe ulcers and £6,249 for patients with more severe ulcers.

The cost of inpatient care for diabetic foot ulcers is difficult to estimate, since some inpatient admissions are a direct result of ulceration whilst others are not, and another proportion of admissions for unrelated conditions may result in ulceration during the hospital stay. It follows therefore that the cost of foot care will vary, from being the major cost-driver in an admission to being a relatively small proportion of the overall cost. Kerr et al. (2014) used an analysis of Hospital Episode Statistics (HES) and approximately 500 Healthcare Resource Groups code (HRG) data to determine the number of admissions for which a foot ulcer was the primary cause and cost-driver. They then used a multiple regression model to calculate the excess length of stay attributable to foot ulcers for those admissions where the ulcer was not the primary cause of the admission. This analysis generated a unit cost per admission detailed in Table 12

Intervention costs

The cost of bespoke orthotic footwear varies considerably, as might be expected with a bespoke intervention. Depending on the individual characteristics of the patient's feet, a more complex orthotic with inserts or mouldings may be required or alternatively a simpler design may be appropriate. A search was conducted of orthotic prices and returned results for 3 NHS sites (East Sussex Trust, Great Western Hospital and Pennine Acute Trust) and this information was shared with the GDG.

Table 11: Intervention costs

Intervention	Average cost
Bespoke or off-the-shelf orthotic footwear, inserts and education on their use	£525 (£250–£800)

After discussion and reference to their own trusts where possible, the GDG agreed an appropriate estimated mean price was £525 (used in the base case), with a range of £250 to £800. This cost, which includes the cost of fitting the shoes, is applied annually according to the assumption that all patients will receive a new pair of bespoke shoes – or similarly expensive repair and maintenance – each year for the remainder of their lifetime.

1 **Table 12: Costs used in the model**

Parameter	Unit cost	Source	Notes
Average ulcer cost for less severe ulcers	£3,221	Kerr et al (2014)	Excludes those patients with ulcers extending to tendon, periosteum or bone, and those with infections of bone, soft tissue infections requiring systemic antibiotics, gangrene, critical renal disease, severe peripheral arterial disease and other complications including Charcot.
Average ulcer cost for more severe ulcers	£6,249	Kerr et al (2014)	Those patients exhibiting the characteristics described above which are not present in less severe patients
Ulceration – Foot Ulcer HRGs	£3,848	Kerr et al (2014)	Based on an analysis of Hospital Episode Statistics (HES) and approximately 500 Healthcare Resource Groups code (HRG) data to determine the number of admissions for which a foot ulcer was the primary cause and cost-driver.
Ulceration – Non-foot-ulcer HRGs (excess length of stay)	£3,038	Kerr et al (2014)	Based on analysis of a multiple regression model used to calculate the excess length of stay attributable to foot ulcers for those admissions where the ulcer was not the primary cause of the admission
Major amputations	£10,907	NHS Reference costs, 2013-14	Mean cost derived from HRG codes YQ21A – YQ22B inclusive.
Minor amputations	£6,720	NHS Reference costs, 2013-14	Mean cost derived from HRG codes YQ24A-YQ26C inclusive
Physiotherapy	Mean cost of £34, (IQR £28-£38)	PSSRU	30 per patient per year (major amp) 10 per year (minor amp) (Kerr et.al 2014)
Wheelchair use	£89 per self or attendant propelled chair per year; £178 per active user per chair per year; £412 per powered chair per year.	PSSRU	Assumed that 50% of patients receive wheelchairs (Kerr et.al 2014)

Parameter	Unit cost	Source	Notes
Prosthetic services	£2,879	Kerr et al (2014)	Assumed that 86% of major amputees referred to prosthetic services (Kerr et.al 2014). Average cost of referral and provision per patient per year for the remainder of their life expectancy. Costs are pro-rata in the model (monthly).
Transport	£32.00 per patient per visit	(Kerr et.al 2014)	Assumed that 50% of patients require NHS transport to attend post-amputation care

J.2.3.16 Health-related quality of life

We conducted a literature search to locate utility values to be applied to the health states in the economic model. A 2010 paper by Redekop et al. provided utility values for each of the disease states used in our model (see Table 13) These values were taken from a survey of the general public in the Netherlands using a variation of the standard time trade-off approach where participants were interviewed in groups (although individual answers were used to make the utility calculations). The respondents were able to practise the time trade-off approach on 3 general health states generated by the EQ-5D instrument before valuing the diabetic foot specific states, which were described using vignettes. These utility values were therefore obtained in a manner broadly consistent with the NICE reference case (National Institute for Health and Care Excellence, 2012).

We used the values from Redekop et al. (2010) as multipliers that we applied to a baseline estimate of utility for a person with type 2 diabetes taken from the UKPDS RCT (Clarke et al. 2002). In the Redekop study, a value of 0.89 was used but it is not clear how this was derived. The UKPDS figure of 0.785 matched the requirement of the NICE reference case, but is lower than the baseline utility used in some type 2 diabetes models and CUAs. This baseline utility value has been adopted in other guidelines, including NICE guidelines on type 1 and type 2 diabetes, and was therefore used here for consistency reasons also.

Table 13: Utility values used in the model

State	Value (95%CI)	Source
Ulcer - amputation -	Reference state	Redekop et. al (2010)
Ulcer + amputation -	0.89 (0.86, 0.91)	
Infected ulcer + amputation -	0.82 (0.79, 0.85)	
Ulcer - minor amputation +	0.87 (0.84, 0.90)	
Ulcer + minor amputation +	0.80 (0.76, 0.84)	
Infected ulcer + minor amputation +	0.75 (0.71, 0.79)	
Ulcer - major amputation +	0.79 (0.68, 0.77)	
Ulcer + major amputation +	0.74 (0.70, 0.78)	
Infected ulcer + major amputation +	0.68 (0.64, 0.72)	
Double major amputation	0.58 (0.53, 0.62)	

J.2.3.17 Summary

All parameters used in the model are summarised in Table 14, including details of the distributions and parameters used in probabilistic analysis.

We selected the distribution for each of the parameters used in the probabilistic sensitivity analysis with reference to the variable type and the availability of reported information. The PSA uses beta distributions for variables denoting a probability, as they are bounded between 0 and 1, where data are reported to estimate the standard error; otherwise a triangular distribution is estimated. Utility values also use a beta distribution, as they are also traditionally confined to values between 0 and 1. The variables which denote continuous quantities are estimated to follow a normal distribution. We modelled the effectiveness of the intervention using a lognormal distribution (more strictly, we parameterised it as a log-odds ratio, and assumed a normal distribution).

Table 14: All parameters in original cost–utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Distribution of patients at each risk level	64% (low risk), 22% (moderate risk), 64% high risk)	Dirichlet	Alphas list (2253;796;477)	Leese (2006)
Ulcer probability at low risk	0.00017	Beta	Alpha 8, Beta 2245	Leese (2006)
Ulcer probability at moderate risk	0.00112	Beta	Alpha 18, Beta 778	Leese (2006)
Ulcer probability at high risk	0.01688	Beta	Alpha 140, Beta 337	Leese (2006)
Effectiveness of intervention (bespoke)	-1.517 (Log OR)	Normal	Mean -1.51777, Std dev 0.264269	Clinical review
Effectiveness of intervention (off-shelf)	-0.872 (Log OR)	Normal	Mean -0.872, Std dev 0.185	Clinical review
Risk of mortality following ulcer	1.89 (HR)	Triangle	1.60,1.89,2.23	Moulik (2003)
Utility values for health states	See table 13	Beta	See table 13	Redekop (2010)
Healing time for neuropathic ulcer	77.7 days	Normal	Mean 77.7, Std dev 7.908	Zimmy et al. (2002)
Healing time for ischaemic ulcer	133 days	Normal	Mean 133, Std dev 8.418	Zimmy et al. (2002)
Probability of amputation at low risk	0.00557	Beta	Alpha 3, Beta 88	Oyibo et al (2001)
Probability of amputation moderate/high risk	0.04940	Beta	Alpha 27, Beta 76	Oyibo et al (2001)
Probability an amputation is major	0.24	Beta	Alpha 25, Beta 79	Oyibo et al (2001)
Increased risk of amputation given history of amputation	1.65	Triangle	1.29, 1.65, 2.11	Lipsky, 2011
Probability of risk increase (low>moderate)	0.0034	Beta	Alpha 38, Beta 121	Partanen et al (1995)
Probability of risk increase (moderate>high)	0.0254	Beta	Alpha 61, Beta 2337	Adler et al. (2007)
Cost of intervention	£525	Triangle	250,525,800	GDG
Cost of more severe ulcer (community/outpatient care)	£6249	Triangle	£3124.5, £6249, £9373.5	Kerr et al. (2014)
Cost of less severe ulcer (community/outpatient care)	£3221	Triangle	£1610.5, £3221, £4831.5	Kerr et al. (2014)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Cost of inpatient care	£3233.27	Triangle	£1616.6, £3233.27, £4849.9	Kerr et al. (2014)
Monthly cost of post amputation care for major amputees	£418	Triangle	£322, £418, £477	Kerr et al. (2014)
Monthly cost of post amputation care for minor amputees	£64	Triangle	£53, £64, £77	Kerr et al. (2014)
Cost of major amputation	£10,907	Gamma	Mean £10,907, Std dev 174.08	NHS reference costs
Cost of minor amputation	£6,720	Gamma	Mean £6,720, Std dev 93.84	NHS reference costs 2013-14

J.2.3.8 Sensitivity analyses

A deterministic, one-way sensitivity analysis was conducted on key parameters and a full probabilistic sensitivity analysis was performed using the parameters and distributions described in table 14.

J.2.3.9 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters.

We estimated probability distributions for all input variables with the exception of the costs of amputation procedures, given that these are fixed costs attached to HRGs. We sourced distribution parameters from the study in which the value was obtained, where possible, or estimated them based on the usual properties of data of that type.

J.2.3.10 Baseline scenario analyses

The model results presented are for a cohort of diabetic patients who undergo a risk assessment at the start of the model. The interventions are supplied to all patients, or targeted according to risk level.

J.2.4 Original cost–utility model – results

J.2.4.1 Base-case cost–utility results

Base-case results are presented in Table 15 and shown on the cost–utility plane in Figure 2. The model suggests that providing bespoke footwear and inserts (and education on the importance of using them) to high-risk patients is cost saving. When the intervention is given to moderate- and high-risk patients, additional QALYs are generated at additional cost, leading to an ICER of approximately £14,000 per QALY. The model suggests that the provision of such footwear to all patients, including those at low risk of ulceration, generates a small average incremental QALY gain; however, this comes at substantial cost, producing an ICER of over £150,000 per QALY.

Table 15: Base-case deterministic cost–utility results – bespoke shoes, orthotic inserts and education on their use

	Absolute		Incremental			Net monetary benefit	
Treatment	**Costs (£)**	**Effects (QALYs)**	**Costs (£)**	**Effects (QALYs)**	**ICER (£/QALY)**	**£20K /QALY**	**£30K /QALY**
High risk only	£4055.23	9.77				£191,304	£289,044
No bespoke orthotics	£4677.53	9.72	£622.30	-0.05	dominated	£189,632	£286,922
Moderate and high risk	£5486.33	9.87	£1431.10	0.10	£13,818.75	£191,944	£290,613
Low, moderate and high risk	£8543.73	9.89	£3057.40	0.02	£151,823.78	£189,290	£288,156

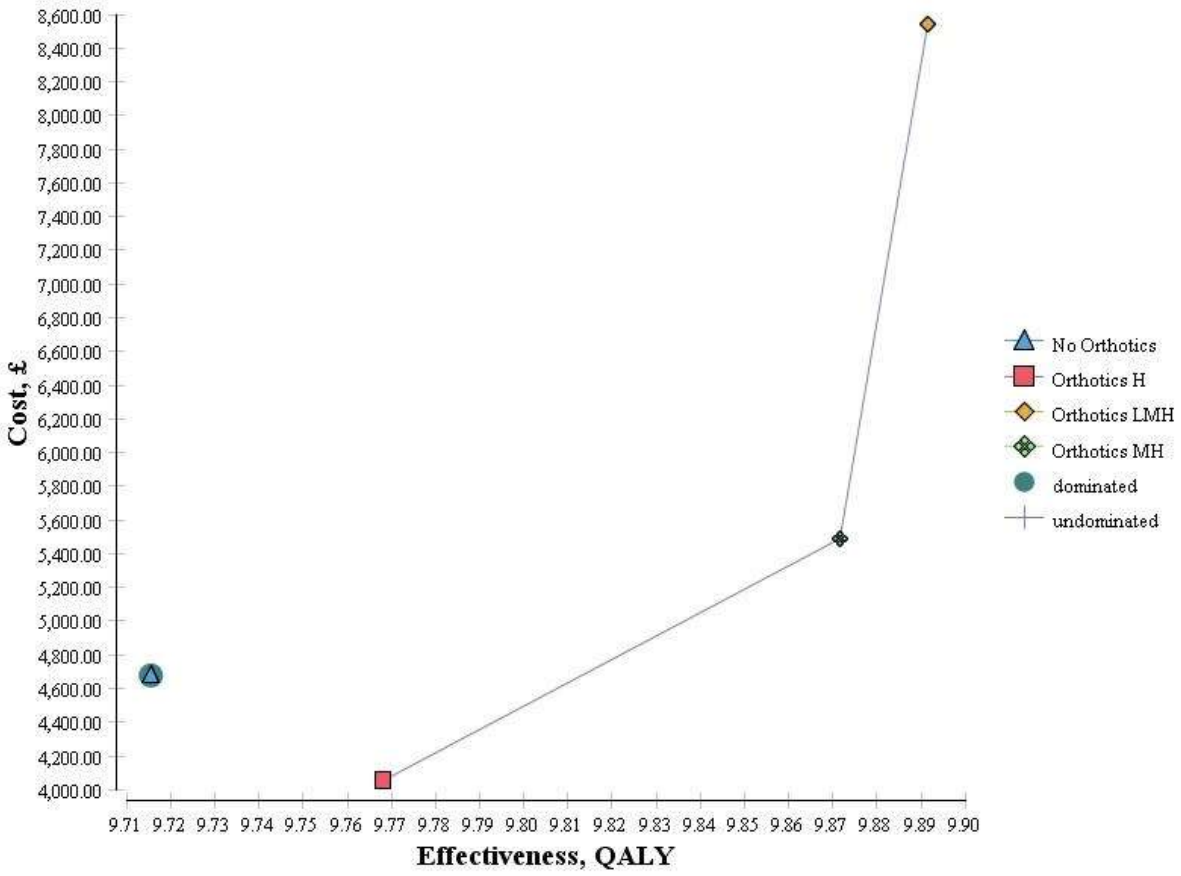

Figure 2: Cost–utility plane

J.2.4.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis suggests that model outputs are driven primarily by the costs and effects (in terms of preventing ulceration) of the interventions themselves. A 1-way sensitivity analysis of costs (Figure 3), given a QALY value of £20,000, suggests that, if the bespoke intervention is cheaper than £82 then the optimal strategy is to provide bespoke footwear and education to all patients, regardless of risk. If the cost is between £82 and £671, the cost-effective strategy is to provide moderate- and high-risk patients with bespoke footwear. Between £671 and £859, the intervention is only cost effective when targeted at

high-risk patients, and at higher costs the intervention is not cost effective at all. In the base case, the mean cost of the intervention was £525.

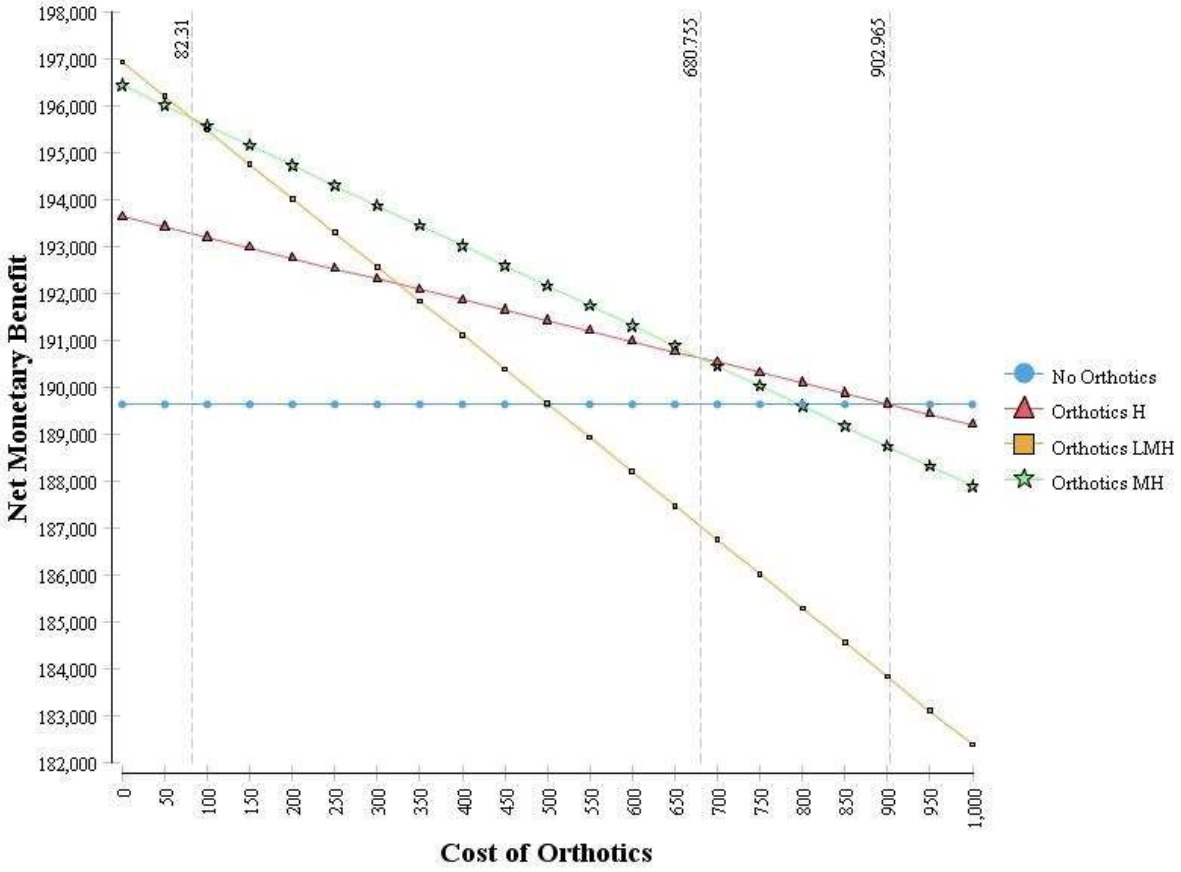

Figure 3 Threshold analysis of costs for bespoke intervention

For the effectiveness of the interventions, we conducted a threshold analysis varying the odds ratio (OR) for ulceration with the intervention between 0–1 (Figure 4). This suggested that, at an OR of less than 0.393, the provision of footwear and education to moderate- and high-risk patients is cost-effective given a QALY value of £20,000. At a narrow range of effectiveness between an OR of 0.393 and 0.403, the analysis suggests that only high-risk patients should be targeted. At lower levels of effectiveness these interventions are not cost effective at all. In the base case the effectiveness (odds ratio) was 0.418 (0.291, 0.601)

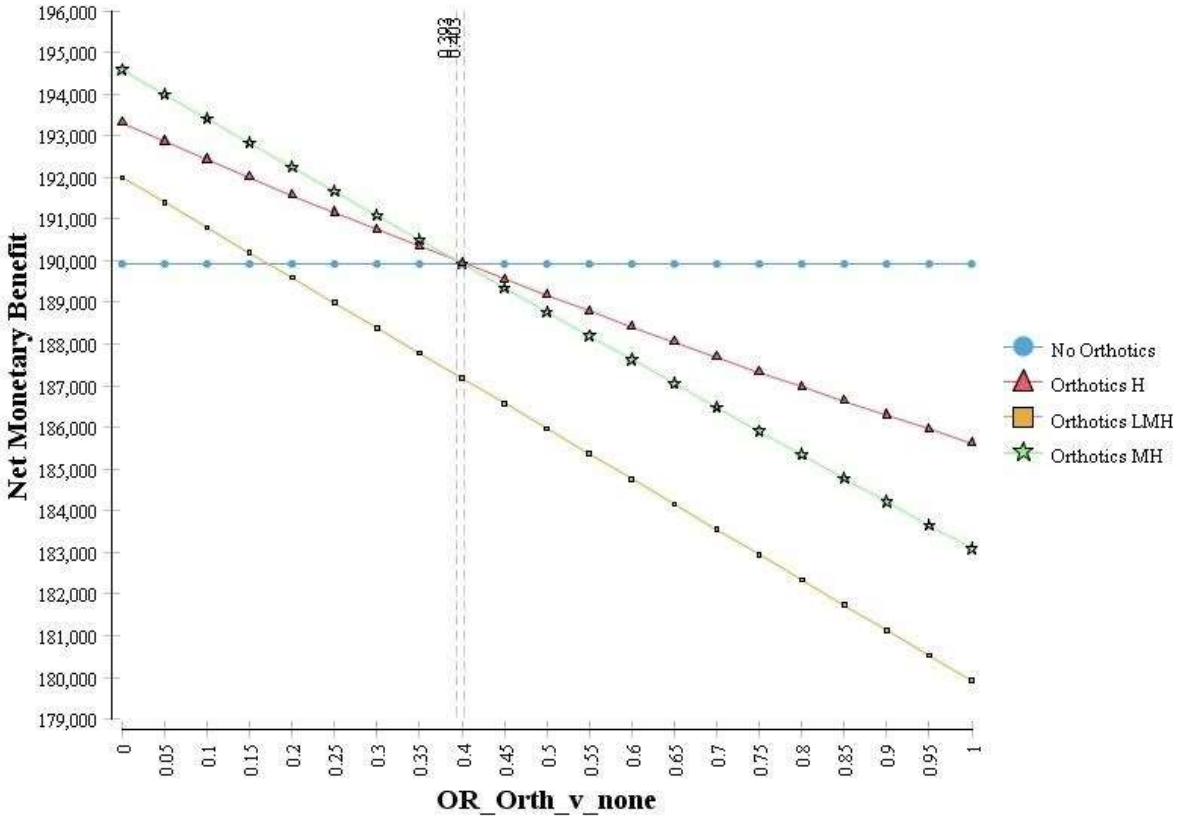

Figure 4 Threshold analysis of effectiveness

J.2.443 Probabilistic sensitivity analysis

A summary of the probabilistic sensitivity analysis, in the form of a cost-effectiveness acceptability curve (CEAC), is shown in Figure 5. This suggests that the provision of bespoke orthotics to people at medium and high risk has a ~75% probability of being cost effective if QALYs are valued at £20,000 each. The mean ICERs and other outputs from the PSA are summarised in Table 16 and are broadly similar to the deterministic results.

Table 16 PSA results for the bespoke intervention

	Absolute		Incremental			Net monetary benefit	
Treatment	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K /QALY	£30K /QALY
High risk only	£4067.38	9.77				£191,251	£289,032
No bespoke orthotics	£4668.27	9.71	£600.89	-0.05	dominated	£189,615	£286,631
Moderate and high risk	£5489.95	9.87	£1422.57	0.10	£13,903.98	£191,874	£290,610
Low, moderate and high risk	£8510.85	9.89	£3020.90	0.02	£151,292.25	£189,253	£288,189

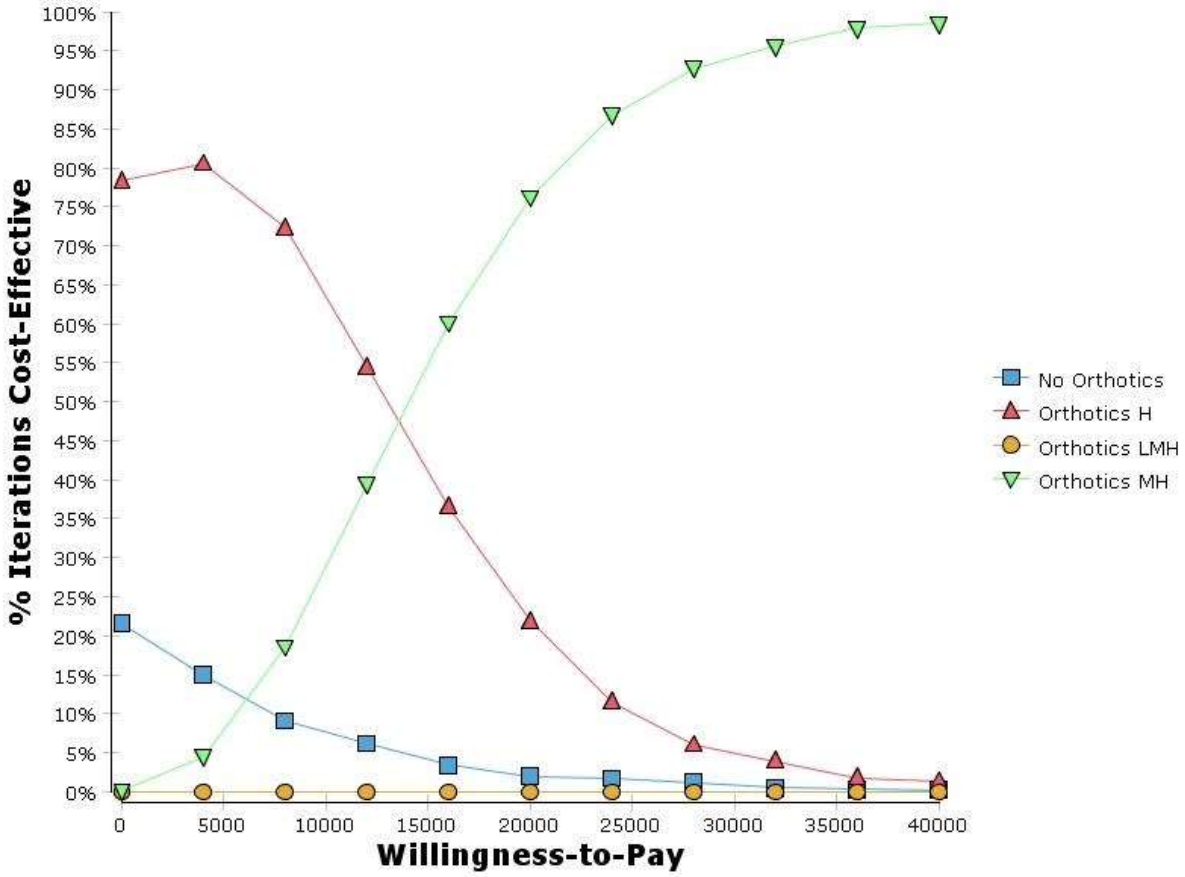

Figure 5: Cost-effectiveness acceptability curve – bespoke shoes, orthotic inserts and education on their use

J.2.4.4 Scenario analysis

In the scenario analysis in which the effects of providing 'off-the-shelf' footwear and inserts (and education on the importance of using them) were explored, results were less favourable (see Table 17 and **Error! Reference source not found.**). The ICER for the scenario in which the intervention is given to high-risk patients is just below £20,000, and the ICER for high- and moderate-risk patients is slightly greater than £20,000 per QALY.

Table 17 Base-case deterministic cost–utility results - "off-the-shelf" shoes, orthotic inserts and education on their use

	Absolute		Incremental			Net monetary benefit	
Treatment	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/ QALY	£30K/ QALY
No Orthotics	£4677.53	9.72				£189,632	£286,922
High risk only	£5411.49	9.75	£733.96	0.04	£19371.63	£189,655	£287,088
Moderate and high risk	£7008.19	9.83	£1596.70	0.08	£20740.53	£189,598	£288,007
Low, moderate and high risk	£10060.93	9.85	£3052.74	0.02	£200,176.66	£186,851	£285,552

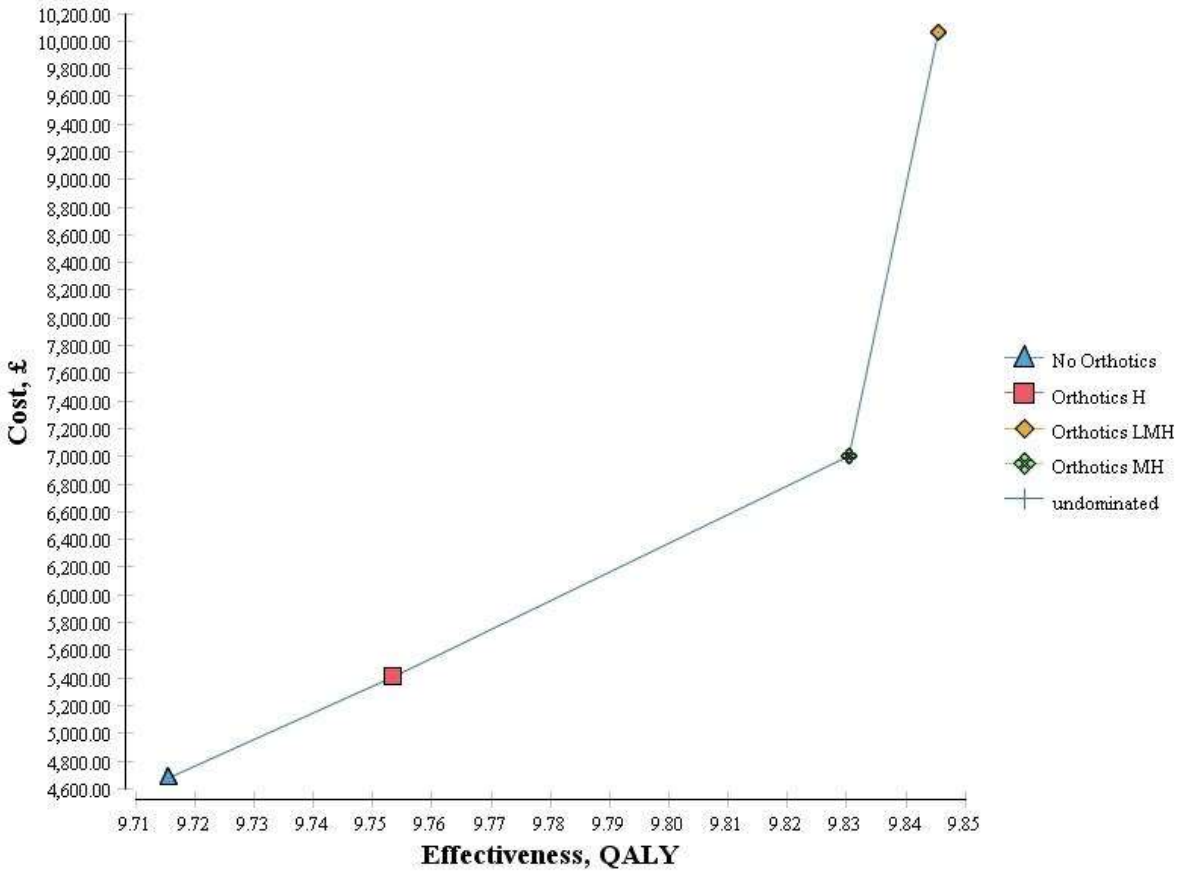

Figure 6: Cost–utility plane

Deterministic sensitivity analysis

For the ‘off-the-shelf’ intervention, a 1-way sensitivity analysis of costs, given a QALY value of £20,000, suggests that, if the intervention is cheaper than £65, then the cost-effective strategy is to provide bespoke footwear and education to all patients, regardless of risk. If the cost is between £65 and £503, the cost-effective strategy is to provide moderate- and high-risk patients with footwear. At higher costs the intervention is not cost effective.

Probabilistic sensitivity analysis

We also repeated our PSA with the ‘off-the-shelf’ effectiveness parameter. The resulting CEAC is shown in Figure 7. It suggests that the provision of off-the-shelf orthotics to people at medium and high risk has an ~40% probability of being cost effective if QALYs are valued at £20,000 each. If the value of a QALY is assumed to be £30,000, off-the-shelf orthotics has a 65% chance of being cost effective. The mean ICERs and other outputs from the PSA are summarised in Table 17 and are broadly similar to the deterministic results.

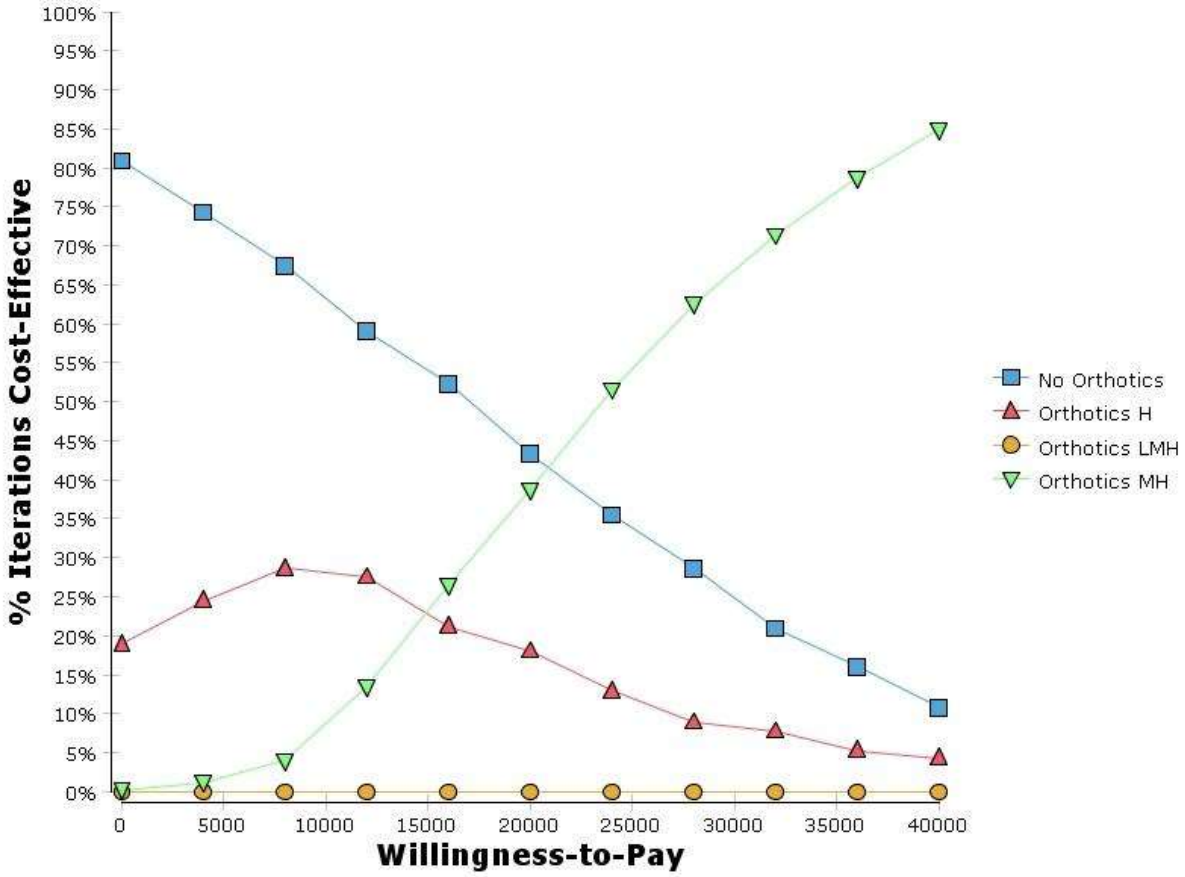

Figure 7: Cost-effectiveness acceptability curve – off-the-shelf shoes, orthotic inserts and education on their use

Table 18 PSA results for the off-the-shelf intervention

Treatment	Absolute		Incremental			Net monetary benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/ QALY	£30K/ QALY
No Orthotics	£4686.09	9.72				£189,697	£286,913
High risk only	£5439.58	9.76	£753.50	0.04	£20,102.57	£189,693	£287,360
Moderate and high risk	£7035.36	9.83	£1595.77	0.08	£21,233.85	£189,600	£287,864
Low, moderate and high risk	£10,064.91	9.85	£3029.56	0.01	£202,455.85	£186,870	£285,435

J.2.5 Discussion

J.2.5.1 Principal findings

The analysis suggests that providing patients who are at moderate and high risk of ulceration with bespoke orthotic footwear is cost effective. Providing high-risk patients with this intervention is cost saving. In the PSA, off-the-shelf orthotics were probably not cost effective

at a threshold of £20,000 per QALY. The model was shown to be sensitive to the effect estimates and the cost of the intervention, with high-cost orthotics only considered cost effective for use in high-risk patients.

Although it does not directly address the different ways in which risk stratification could be performed as a decision problem, our model also provides evidence that dividing the population into risk-specific strata is a theoretically sensible thing to do. The model suggests that risk stratification could result in the effective targeting of resources so that total costs could be managed (or even reduced) compared with strategies in which everyone or no one received preventative care. Therefore, although the model concentrated on a single intervention (the provision of orthotic footwear), it could also be seen as providing economic support for the notion of risk stratification more broadly.

J.2.52 Strengths of the analysis

The analysis has demonstrated the utility of targeting bespoke orthotic footwear interventions for diabetic patients according to their risk factors for ulceration. The model captures a complex disease process in a simplified framework whilst preserving important elements of external validity, including important outcomes of ulceration and amputation.

J.2.53 Limitations of the analysis

The model is a simplification of the diabetic foot disease process. Several large studies on risk factors for diabetic foot ulceration exist based on cohorts such as the Seattle Diabetic Foot Study (Boyko et al. 1999). The development of these individual covariates was not modelled owing to a lack of data on incidence rates needed to parameterise them in the model. Diabetes and diabetic foot problems represent a complex disease process involving patient, limb and ulcer related characteristics and histories which requires simplification to meet the assumptions of a Markov framework. An individual patient model would be a suitable vehicle for a more complex analysis of these factors, but currently this is hampered by lack of data. We capture these individual risk factors by assigning patients to a risk class at the beginning of the model, and then factor in any increase of risk as a function of neuropathy and PVD development over time. In reality, not all patients will attend a risk assessment and will therefore develop a diabetic foot problem unknown to care services. These patients will possibly present at a more advanced stage of disease and be more likely to undergo an amputation. The exclusion of these patients is a limitation of our analysis.

One limitation of our analysis is the imprecise costing of the interventions. We tried to ascertain the costs of a typical off-the-shelf orthotic shoe but these data are often commercial in confidence or unavailable. We asked the GDG for an estimate of costs, which they emphasised would vary greatly depending on the materials used and the complexity of the shoe, but would likely fall within the range we used to parameterise the cost of bespoke shoes and would not exceed that range. In light of the lack of further available data we explored the uncertainty around the cost of these interventions using a threshold analysis. A more precise estimate of these costs would allow a fully incremental analysis to be performed.

Prevention methods are only effective if they are used correctly by the patient. The model assumes that adherence in practice will match that seen in the trials from which effectiveness evidence was drawn; we acknowledge that trial participants may be more motivated to follow the advice of their healthcare practitioners than ‘real world’ patients.

J.2.54 Comparison with other CUAs

Previously published CUAs did not address the specific interventions considered here; therefore there is a lack of a clear reference point for this analysis.

J.2.16 Conclusions

The analysis suggests that providing patients who are at moderate and high risk of ulceration with bespoke orthotic footwear is cost effective. Providing high-risk patients with this intervention is cost saving. In the base-case analysis, off-the-shelf orthotics were just cost effective at a threshold of £20,000 per QALY, but were not considered cost effective in the probabilistic sensitivity analysis. The model was shown to be sensitive to the effect estimates and the cost of the intervention, with high-cost orthotics only considered cost effective for use in high-risk patients.

J.3 Adjunctive treatments for diabetic foot problems

See section 4.12 of the full guideline for details of the review question.

J.3.1 Systematic review of published cost–utility analyses

J.3.1.1 Methods

We conducted a systematic literature search in order to identify published cost–utility analyses that provide evidence of the cost effectiveness of the interventions in question.

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of adjunctive treatments in treating diabetic foot problems.

Search strategy

The search strategy was based on that used to identify clinical evidence for these questions, with the RCT filter removed and a standard economic filter applied (see appendix D).

Quality appraisal

Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the Guidelines Manual (2013).

J.3.1.2 Results

Study identification

We identified 58 studies of potential relevance through title and abstract screening. On perusal of the retrieved papers, 2 cost–utility analyses were identified which considered adjunctive therapies consistent with those identified in the review protocol for RQ11: 1 addressed hyperbaric oxygen therapy and the other focused on the use of a platelet-rich plasma gel.

In addition to these analyses, the GDG reviewed the results of 2 exploratory cost–utility analyses that had been performed to support one of the guidelines that is being updated and replaced by this guideline (NICE clinical guideline 119, 2011). The 2 analyses address hyperbaric oxygen therapy and negative pressure wound therapy. Because the GDG did not prioritise this question for original health economic analysis in the present update, we did not update or revise the analyses from CG119; instead, they were treated as any other pre-existing health economic evidence, and subject to the same quality assessment. The appendix from CG119 detailing the methods and results of these analyses is reproduced below (appendix J.4), as it has not been published elsewhere.

Quality and results of included studies

Details of the design, quality and results of included studies are tabulated in Table 19.

Table 19: Economic evidence table – hyperbaric oxygen therapy versus standard care

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Guo et al (2003) Hypothetical cohort 1000 diabetics 60yrs old, Wagner's Class III or above. USA. **Partially applicable[a]** **Very serious limitations[b,c,d,e,f]**	Effects: Based on 4 small prospective controlled studies. 3 of these excluded from our clinical evidence. Costs: surgery, impatient care, rehabilitation, first-year outpatient visits & physician fees. Sources & figures not explicitly documented in the text. USA health service and societal perspective Utilities: Taken from published HrQol studies of diabetes	Decision tree model. Conventional wound care (definition unclear) vs conventional wound care + HBO_2 All patients receiving HBO_2 considered eligible (i.e. no contraindications or side effects of treatment considered). Outcomes were healing rates and amputations Unclear if a full systematic review of clinical evidence was undertaken.			ICER at year 1 = $27,310 per QALY Year 5 = $5,166 per QALY Year 12 = $2,255 per QALY	HBO_2 therapy in the treatment of diabetic ulcers is cost-effective, particularly based on a long-term perspective	No PSA undertaken Best/Base/Worst case scenarios modelled by varying the rate of healing and minor/major amputation rates (based on studies excluded from the clinical review). ICER ranges from $142,923, $27,310 to -$72,799 at year 1 in the worst/base/best scenario. V sensitive to effect estimates from limited (poor quality) evidence base.

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
NICE (2011) 'those with diabetic foot problems who require adjunctive therapies… assumed [to be]… the more severe cases' UK **Directly applicable** **Very serious limitations**[g,h,i,j,k]	Effects: Stated as meta-analysed from RCTs, but derivation not reported Costs: Sought from relevant NHS providers HBO_2: 30 sessions @ £168 = £5040 Utilities: EQ-5D from a postal survey of 440 patients with type 1 or type 2 diabetes	Decision tree Authors call analysis 'highly exploratory' and note that it 'utilises methods and data that might not usually be done in a full high quality review'	HBO_2: £11,250 Standard care: £9600	HBO_2: 0.409 QALYs Standard care: 0.477 QALYs	HBO_2 -v- standard care: £24,486/QALY	HBO_2 'associated with ICERs greater than what is considered cost effective'	Probability that HBO_2 is cost-effective: @WTP £20K/QALY = 0.44 @WTP £30K/QALY = 0.54 Alternative utility values raise ICER Authors note 'for HBO_2, the cost is the key variable' (no further details given).

a Non- UK/NHS setting
b Based on small trials, many excluded from the clinical evidence base for this question.
c No PSA
d Model is highly sensitive to effect estimates, which are sourced from poor quality evidence
e Poorly defined comparator of conventional wound care – not explicit
f Unclear how effect estimates were derived and whether a full systematic review of the literature was undertaken
g Model structure limited to one foot and omits critical aspects of health condition (mortality; recurrent ulcers)
h Time horizon (1 year) too short to capture important differences
i Derivation of relative effects unreported
j Cost estimates omit important components (capital costs of new facilities and/or transport costs to use existing facilities)
k Invalid parameterisation of beta distributions for relative effects in PSA

Table 20: Economic evidence table – platelet-rich plasma gel versus standard care

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Dougherty (2008) Platelet rich plasma gels v alternative therapies. Hypothetical cohort of 10,000 patients. USA. **Partially applicable**[a] **Very serious limitations**[b,c,d,e,f,g,h]	Effects: Single PRP randomised control trial (Driver et. al. rated as v. low quality) Costs: Sourced from manufacturer and distributors of PRP Utilities: Indirect. Adapted from HAD measurements	PRP plasma gel + GWC v Saline Gel + GWC (good wound care) Outcomes of interest were wound healing rates and amputations	$15,159	2.87 QALY	PRP dominates	PRP is a dominant therapy option compared to saline gel and good wound care	No incremental analysis of alternative therapies, although comparative estimates of cost effectiveness are given but apparently not modelled (PRP dominates all options). Unclear where reported QALY values for comparison sourced from. Sensitivity analysis only varied the cost of PRP.

a non- UK/NHS setting
b based on limited, low quality trial evidence
c Not a fully incremental analysis, but alternative comparators mentioned in discussion
d sensitivity analysis only considers cost of PRP
e No PSA
f Uses a mental health index to measure quality of life impacts
g poorly defined comparator of good wound care – not explicit
h unclear how effect estimates were derived and whether a full systematic review of the literature was undertaken

Table 21: Economic evidence table – negative pressure wound therapy versus standard care

Study, Population, Country and Quality	Data sources	Other comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
NICE (2011) 'those with diabetic foot problems who require adjunctive therapies… assumed [to be]… the more severe cases' UK **Partially applicable**[a] **Very serious limitations**[b,c,d,e]	Effects: Stated as meta-analysed from RCTs, but derivation not reported Costs: Sought from relevant NHS providers. NPWT = £420 x 4 wk = £1680 Utilities: EQ-5D from a postal survey of 440 patients with type 1 or type 2 diabetes	Decision tree Authors call analysis 'highly exploratory' and note that it 'utilises methods and data that might not usually be done in a full high quality review'	NPWT: £5512 Standard care: £4542	NPWT: 0.494 QALYs Standard care: 0.474 QALYs	NPWT -v- standard care: £49,691/QALY	NPWT 'associated with ICERs greater than what is considered cost effective'	Probability that NPWT is cost-effective: @WTP £20K/QALY = 0.15 @WTP £30K/QALY = 0.26 Alternative utility values raise ICER Authors note 'if the cost of NPWT is very low and the cost of amputation is very high then NPWT could be cost effective' (no further details given).

a Substantial reductions in cost of intervention since analysis was conducted
b Model structure limited to one foot and omits critical aspects of health condition (mortality; recurrent ulcers)
c Time horizon (1 year) too short to capture important differences
d Derivation of relative effects unreported
e Invalid parameterisation of beta distributions for relative effects in PSA

J.3.113 Discussion

1 partly applicable CUA with very serious limitations, based on a decision tree structure, found that HBO2 therapy in the treatment of diabetic ulcers is cost-effective based on a long-term perspective. The analysis does not provide a clear breakdown of cost assumptions and this, along with its U.S setting, makes it difficult to translate into an NHS context.

1 partly applicable CUA with very serious limitations found that platelet rich plasma gels combined with good wound care dominated saline gels and good wound care. The lack of a fully incremental analysis, non-UK setting, and very limited quantification of uncertainty means the findings of this study should be interpreted with caution.

1 directly applicable CUA with potentially serious limitations from a UK, NHS and PSS perspective found that HBOT and NPWT were not cost effective at a QALY value of £20,000 and suggested that the costs of these interventions were the main driver of this finding.

J.4 2011 original modelling – adjunctive therapies for the treatment of diabetic foot problems

As noted in J.3.1.2 above, the GDG reviewed the results of 2 exploratory cost–utility analyses that had been performed to support NICE CG119 (2011). The appendix from CG119 detailing the methods and results of these analyses is reproduced verbatim in this section, as it has not been published elsewhere. We have not performed any revision or updating of these analyses as part of the present update.

J.4.1 Introduction

NICE has been asked to produce a guideline on the management of diabetic foot problems. As part of this guideline two adjunctive therapies were considered: negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT). What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in coming to recommendations. The quality of the data would usually preclude conducting an analysis given the poor quality of the clinical evidence. However, the GDG considered that cost effectiveness analysis would be required to help finalise recommendations. Where possible, this analysis has been conducted according to NICE methods outlined in the 'Guide to the methods of technology appraisals' (2008) and the 'Guidelines manual' (2009). Therefore, it attempts to follow the NICE reference case (the framework NICE requests all cost effectiveness analyses to follow) in the methodology utilised. It is advised that the full guideline should be read, as full definitions of terminology will be given there.

Given the paucity of available information, GDG opinion was used in the identification and selection of papers and data. In addition, the results presented should be considered exploratory given the significant issues in the quality of data and assumptions made.

J.4.2 Decision problem

The decision problem is described in Table 22.

Table 22 Decision problem

	Approach taken
Population	People with diabetic foot problems
Interventions	HBOT NPWT
Comparators	Standard care without HBOT and NPWT
Outcome(s)	Cost per QALY

J.4.2.1 Population

The population in this analysis represents those with diabetic foot problems who require adjunctive therapies. It can be assumed that these represent the more severe cases of diabetic foot problems since standard care would be sufficient for the majority of people.

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J.4.2 Interventions

The two adjunctive therapies to be considered are HBOT and NPWT. These will be considered in combination with standard care. For this guideline these interventions will be examined as a class of interventions and individual types will not be examined.

J.4.3 Comparators

The comparator will be standard care alone

J.4.3 Literature search

A literature search was carried out and a search was conducted for UK specific cost effectiveness papers. This approach was chosen since it is very difficult to extrapolate from papers from other countries. No UK-specific cost effectiveness papers were identified for either HBOT or NPWT. There are three identified papers on HBOT: Chuck et al 2008, Hailey et al 2007 and Guo et al 2003. The Guo et al 2003 paper provided the structural basis for all the models. However, it is difficult to identify the data sources that went into the model. In addition, it is not clear how long-term outcomes were incorporated into the model. No Markov model was included; instead it appeared that people stayed in the same state as they did at the end of year 1. So someone healed at the end of year 1 remained so for the whole analysis. This could result in overestimating the benefits of treatment since it does not include any further hospitalisation or amputations. Therefore, a new analysis will be run with NHS-specific costs and clinical outcomes based on the clinical review.

J.4.4 Model structure

The model structure is summarised in Figure 8:

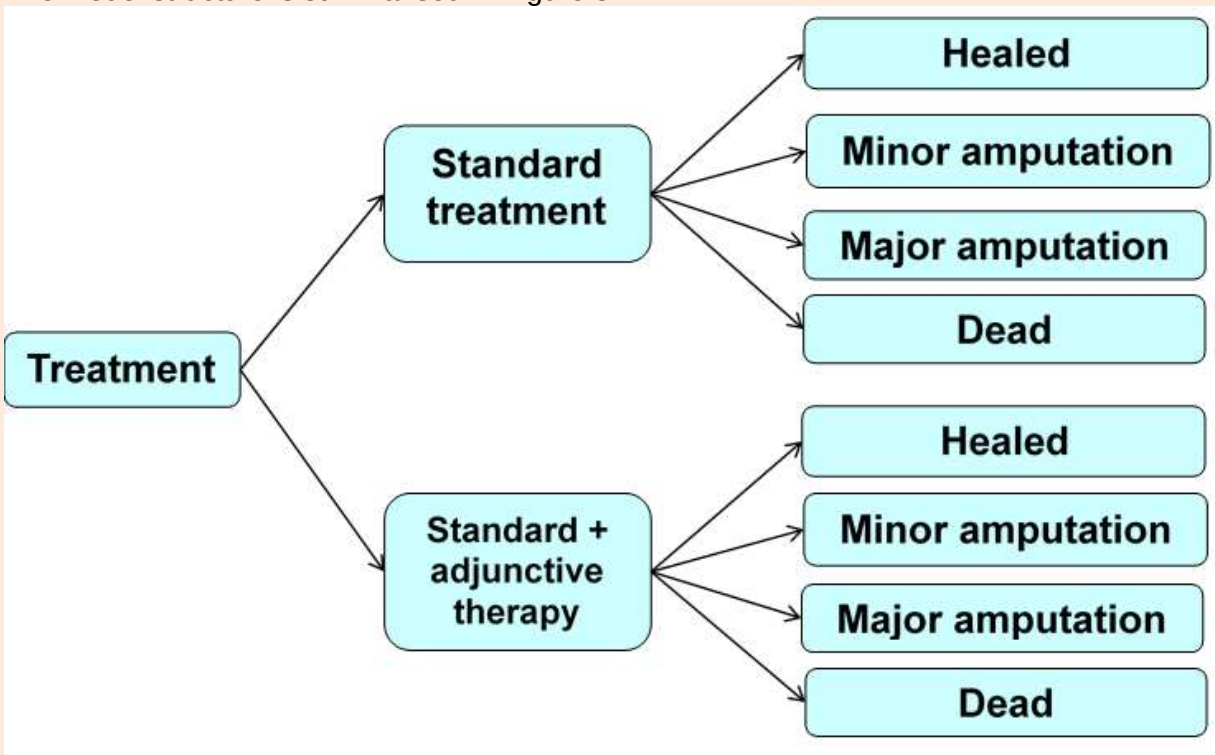

Figure 8 Model structure for adjunctive therapies

A decision tree was chosen because it covers the key outcomes for treatment, which is to improve immediate outcomes (i.e. amputations and so on). It is also the same structure used in Guo et al 2003 and Chuck et al 2008.

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The outcomes chosen were based on work for diagnosing osteomyelitis (see appendix I). If data are not available on minor and major amputations, these two outcomes will be merged into one health state: amputations. The reason for not considering long-term outcomes via a Markov model was that there has been no long-term data on the effect of the treatments. This is covered in greater detail in the assumptions section.

J.4.5 Assumptions

J.4.5.1 Time horizon

The model did not include long-term outcomes. The reason for this was that there was a lack of data on the patient group. Attempts to attach Markov states to the decision tree resulted in difficulties including the appropriate costs and issues regarding the comparability of the patient groups. Alternative considerations included including a long-term outcome variable based on the expected survival of someone with diabetic foot problems and relating them to the various outcomes and then using this figure to calculate a lifetime QALY value. This could then be combined with the expected costs of treatment to give an estimate of the lifetime cost per QALY. However, no estimates for a number of the key variables, including the lifetime costs for someone with a healed ulcer, was possible and therefore could not be included. The effect this has on the validity of the results will be discussed in the limitations section.

J.4.5.2 Treatments have no effect on mortality

The clinical effectiveness review did not find evidence for the adjunctive therapies having any effect on mortality. In part this was caused by the studies not recording mortality as an outcome. Therefore, mortality will be assumed to not be affected by treatment.

J.4.5.3 No quality of life impact of treatments

There was no evidence identified by the clinical review on the adverse events or quality of life effect of adjunctive therapies. Therefore, it will be assumed that they have no effect on quality of life.

J.4.6 Inputs

J.4.6.1 Clinical outcomes

The clinical outcomes for the adjunctive treatments will be based on the conclusions of the clinical review. For both treatments a meta-analysis was conducted and this will be the basis of the clinical outcomes. A summary is provided in Table 23 for both adjunctive treatments.

Text reproduced from 2011

Table 23 Clinical outcomes for adjunctive treatments

Outcome (%)	HBOT analysis		NPWT analysis	
	Standard therapy	HBOT and standard care	Standard therapy	NPWT and standard care
Healed	15.6	63.2	73.6	80.34
Minor amputation	35.1	13.5	10.4	3.66
Major amputation	24.67	6.96		
Dead	16	16	16	16

There was no evidence that there is any effect on mortality. However, it is a recorded outcome of diabetic foot management. Though mortality will be excluded for the base case, sensitivity analyses will include mortality and various relative risks applied to represent potential reductions in death.

J.4.6.7 Utilities

The utilities were extrapolated from the diagnosis of osteomyelitis model. The base-case values are reproduced below in Table 24. Sensitivity analysis will be conducted using values from Ortegon et al 2004 and Sullivan et al 2002.

Table 24 Utility values included in model

Health state	Value
Primary healing	0.6
Healed after minor amputation	0.61
Healed after major amputation	0.31

J.4.7.8 Cost

The cost of amputations (major and minor) and standard treatment were extrapolated from osteomyelitis model (see appendix I). When amputations were merged into one state the cost was averaged. This may under/overestimate the cost impact given the relative proportion between minor and major amputations. The remaining variables that need defining are the cost of HBOT and NPWT.

J.4.8.7.1 Hyperbaric oxygen therapy

The NHS reference cost for HBOT states that a day case is £288 per session. Evidence from NORCOM (North Derbyshire, South Yorkshire and Bassetlaw Commissioning Consortium) suggests that the average cost for 30 sessions is approximately £8000. According to NHS Quality Improvement Scotland, the average number of sessions is approximately 30, with a maximum of 40. Estimates obtained during consultation from providers of HBOT gave a much lower estimate of £168 per session. Given that this figure comes directly from providers it will be used in the base-case analysis. Sensitivity analysis of 50% will be conducted around this figure.

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J.4.8 Negative pressure wound therapy

There is no publicly listed price for NPWT and the GDG noted that there are a number of suppliers whose costs vary greatly.

NHS Yorkshire conducted an analysis when writing local specification for the provision of NPWT locally. This gave the cost per dressing for various systems and estimated the cost of weekly treatment to be £420. This was presented to the GDG and considered to be reflective of the true cost. This was then multiplied by the expected length of treatment of 4 weeks giving a total cost of £1680. The GDG considered this to be a reasonable estimate.

J.4.9 Summary of variables

Table 25 Variables included in probabilistic analysis

Variable	Mean	Lower limit	Upper limit	Distribution	A	B
Adjunctive therapy						
Hyperbaric oxygen therapy	5040	2520	7560	Uniform	N/A	N/A
Negative pressure wound therapy	1680	420	6720	Uniform	N/A	N/A
Utilities						
Healed	0.6	0.5	0.8	Beta	60	40
Minor amputation	0.61	0.4	0.8	Beta	61	39
Major amputation	0.31	0.2	0.6	Beta	31	69
Costs						
Standard treatment	3458	2000	15000	Gamma	1.65	2102
Minor amputation	5939	200	10000	Gamma	4.99	1485.25
Major amputation	14038	5000	25000	Gamma	3.99	3519.51

J.4.10 Results

J.4.10.1 Deterministic and probabilistic results

The results are presented in Table 26 and Table 27.

Table 26 Base case results for NPWT

	QALY	Cost (£)	Incremental QALYs	Incremental Costs (£)	ICER (£)
Deterministic					

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Standard	0.4740	4542	-	-	-
NPWT	0.4935	5512	0.0195	970	49691
Probabilistic					
Standard	0.4728	4550	-	-	-
NPWT	0.4923	5541	0.0195	991	50821

Table 27 Base case results for HBOT

	Cost (£)	**QALY**	**Incremental Costs (£)**	**Incremental QALYs**	**ICER (£)**
Deterministic					
Standard	9599.6	0.4094			
HBOT	11250	0.4773	1650.4	0.0674	24,486
Probabilistic					
Standard	9621	0.4091			
HBOT	11318	0.4764	1697	0.0673	25,215

Both these analyses indicate that NPWT and HBOT are associated with ICERs greater than what is considered cost effective.

J.4.10.2 Sensitivity analysis

One-to-one sensitivity analysis

The deterministic sensitivity analysis indicates that for HBOT, the cost is the key variable. For NPWT, the results indicate that if the cost of NPWT is very low and the cost of amputation is very high then NPWT could be cost effective.

Utility sensitivity analysis

Given the apparent inconsistency in the healed and minor amputation states, two additional utility estimates were used. The results are presented in Table 28 and Table 29.

Table 28 Utility sensitivity analysis - HBOT

	QALY	**Cost (£)**	**Incremental QALYs**	**Incremental Costs (£)**	**ICER (£)**
Sullivan et al 2002					
Standard	0.6043	9600	-	-	-
HBOT	0.6599	11250	0.0556	1650	29689
Ortegon et al 2004					

Text reproduced from 2011

Standard	0.5512	9600	-	-	-
HBOT	0.5652	11250	0.0140	1650	118003

Table 29 Utility sensitivity analysis - NPWT

	QALY	**Cost (£)**	**Incremental QALYs**	**Incremental Costs (£)**	**ICER (£)**
Sullivan et al 2002					
Standard	0.6818	4542	-	-	-
NPWT	0.6973	5512	0.0155	970	62654
Ortegon et al 2004					
Standard	0.5650	10146	-	-	-
NPWT	0.5690	14445	0.00404	4299	240175

Cost effectiveness planes

Figure 9 and Figure 10 are the cost effectiveness planes for HBOT and NPWT. These results indicate that the majority of the simulations are in the northeast quadrant, but it is possible that these interventions could be cost saving. However, the spread indicates that there is variation in the effectiveness and costs.

Figure 9 Cost effectiveness plane - HBOT

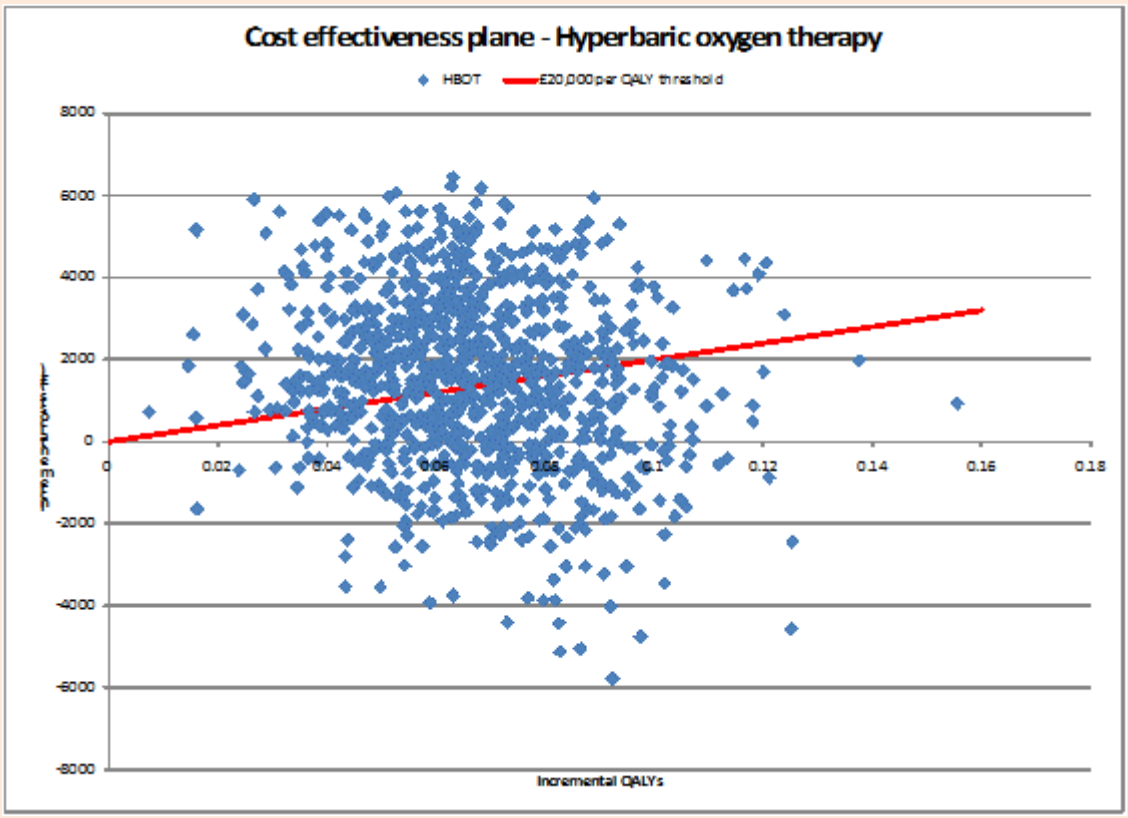
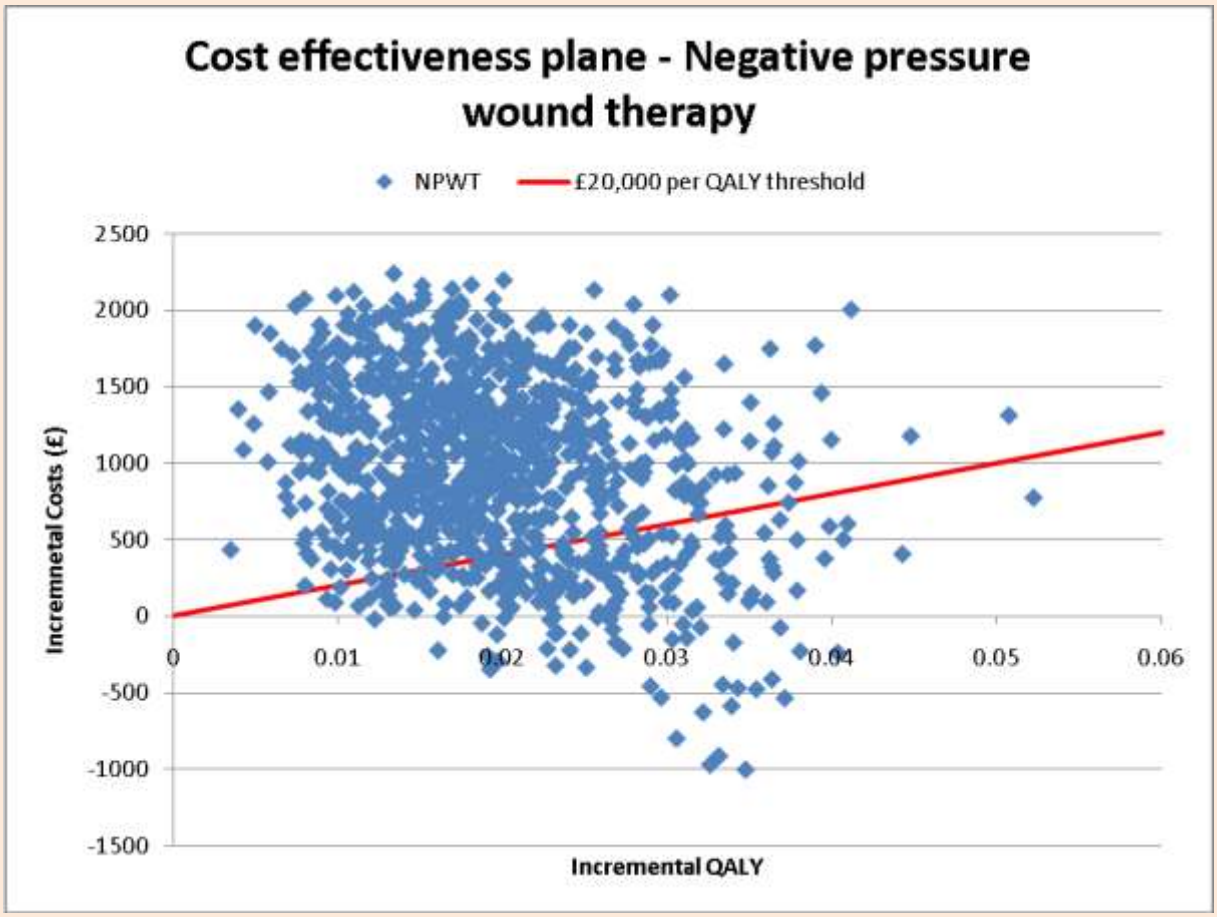


Figure 10 Cost effectiveness plane - NPWT



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Cost effectiveness acceptability curves

The cost effectiveness curves for HBOT in Figure 11 and NPWT in Figure 12.

Figure 11 Cost effectiveness acceptability curve - HBOT

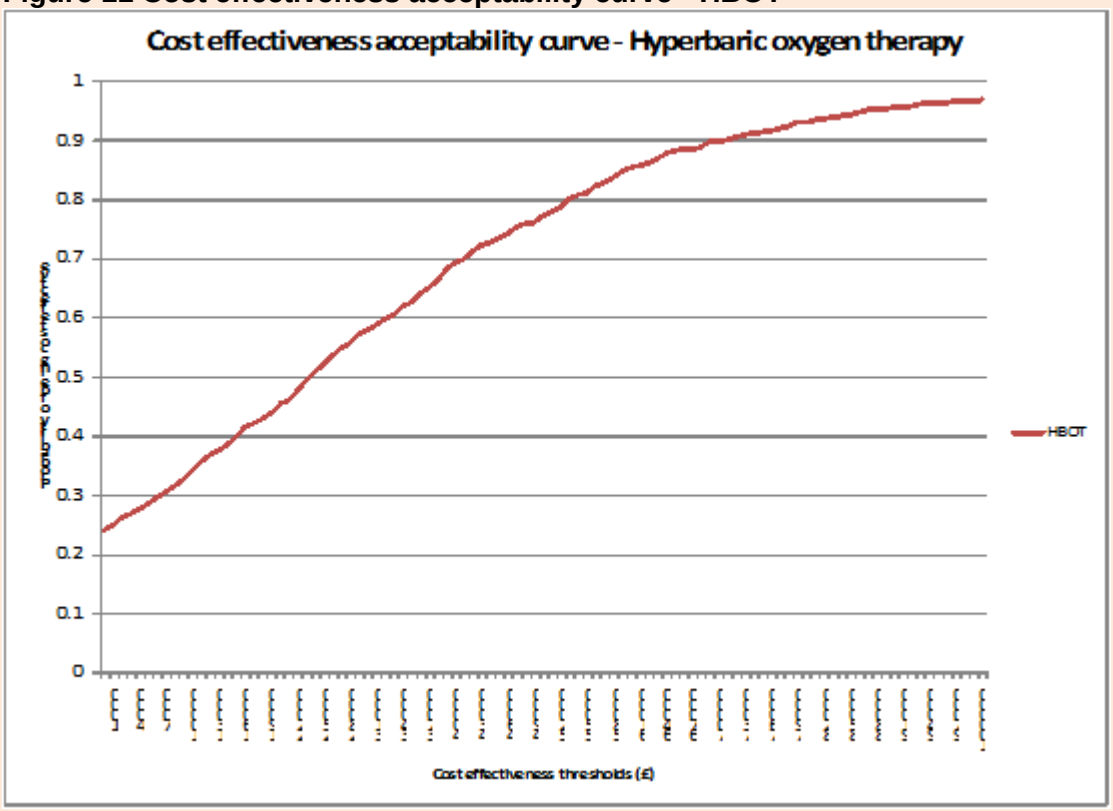

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Figure 12 Cost effectiveness acceptability curve - NPWT

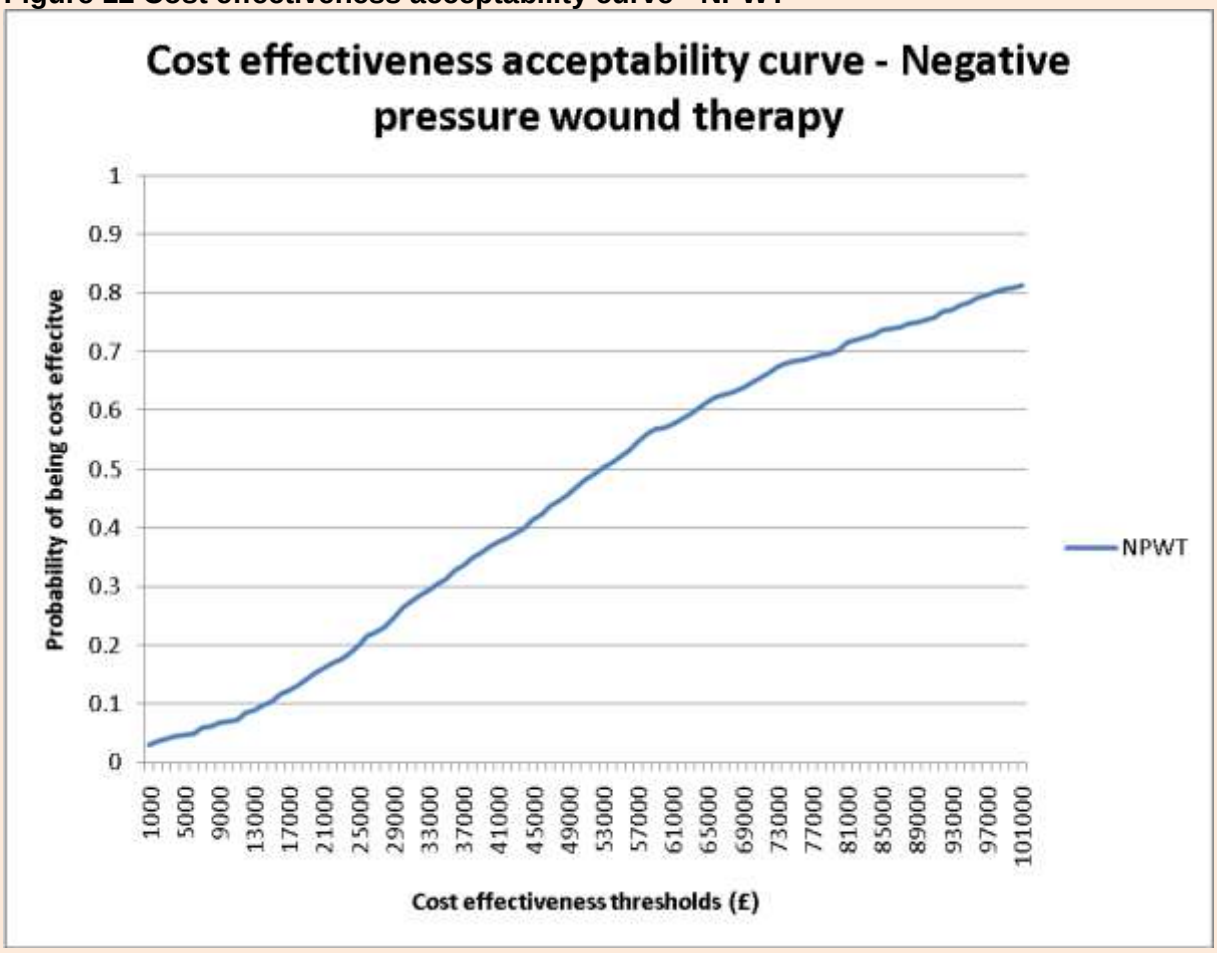

Table 30 Probability of being cost effective at different thresholds

Threshold	HBOT	NPWT
£20,000	0.44	0.152
£30,000	0.54	0.264

These results indicate that these treatments are associated with considerable uncertainty.

J.4.1.1 Limitations

J.4.1.1.1 Clinical data

The clinical data included in the analysis was generally of poor quality, and therefore the model is only as reliable as the data being inputted into it. This is especially true for the NPWT model where there was no data on its use in preventing primary amputations. Improved evidence of clinical effectiveness is required to help justify its use.

In addition, there was no clinical data identified on the effect these therapies have on mortality, and therefore potential benefits may not have been accounted for in the model.

J.4.1.1.2 No long-term outcomes

The model did not include long-term outcomes. The reason for this was that there was a lack of data on the patient group. Attempts to attach Markov states to the decision tree resulted in difficulties including the appropriate costs and issues regarding the comparability of the patient groups. Alternative considerations included including a long-term outcome variable

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based on the expected survival of someone with diabetic foot problems and relating them to the various outcomes, and then using this figure to calculate a lifetime QALY value. This could have then be combined with the expected costs of treatment to give an estimate of the lifetime cost per QALY. However, no estimates for a number of the key variables including the lifetime costs for someone with a healed ulcer was possible and therefore could not be included. This is a major limitation since people who have amputations generally have worse outcomes than those who don't. As such, the benefits of the treatments may have been underestimated. Future work should look to properly address this by constructing a full decision tree and Markov model.

J.4.11.3 Costs

The costing was based on aggregate values from NHS reference costs. Other than the cost of the adjunctive therapies no other costs were included. Therefore, potential cost differences may have been excluded, for example any difference in hospital stay or additional medication given. The effect of this limitation on the cost effectiveness results is unknown.

J.4.12 Discussions and conclusions

The analysis constructed was highly exploratory and based on a simple model and has several limitations. Therefore, this economic analysis should not be considered to be a full cost effectiveness analysis, but exploratory to examine the potential impact of recommending adjunctive therapies. This analysis utilises methods and data that might not usually be done in a full high quality review.

Analyses by Chuck et al 2008 and Guo et al 2003 indicated that HBOT in particular could be potentially cost effective; however, both of these analyses used longer time horizons, which indicates that it is possible that the treatments could be cost effective if long-term outcomes are included. However, it is not clear in which patient group these treatments will be used in, therefore which set of long term outcomes to use.

The analysis conducted is highly uncertain; however, it does indicate that there is potential benefit of the treatments, especially for NPWT where the data is of very poor quality.

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J.4.14 References

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